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Edited by A. L. BACHARACH, M.A.(Cantab), F.R.I.C. and THEODORE RENDLE, F.R.I.C.

With an Introduction by SIR JOSEPH BARCROFT, C.B.E., F.R.S.

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Some thirty authors have contributed to this book. Many of them are well known for their original contributions in the fields of biochemistry or food technology. They come from laboratories at academic centres, at government research institutions and at food factories. The book thus represents a piece of scientific collaboration by experts selected without any consideration other than their ability to assemble information and give it accurate expression. The authors have brought together all the knowledge at present available about the composition of the foods, and therefore the diets, of the British people. This has involved a detailed examination of seven main foods or groups of foods and the recording of innumerable data giving their chemical compositions.

The widest possible view has been taken as to the meaning of the words "chemical composition"; besides including vitamins, amino-acids and other constituents of less clear function (nucleo-tides, nitrogenous bases and so on), authors have given attention to the physical properties of the foods and also to the effect on them of cooking and processing. Based on a series of lectures given in war-time Britain, the seven parts of this book have much more than an ephemeral value.

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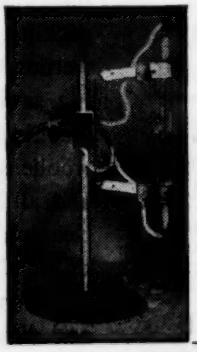

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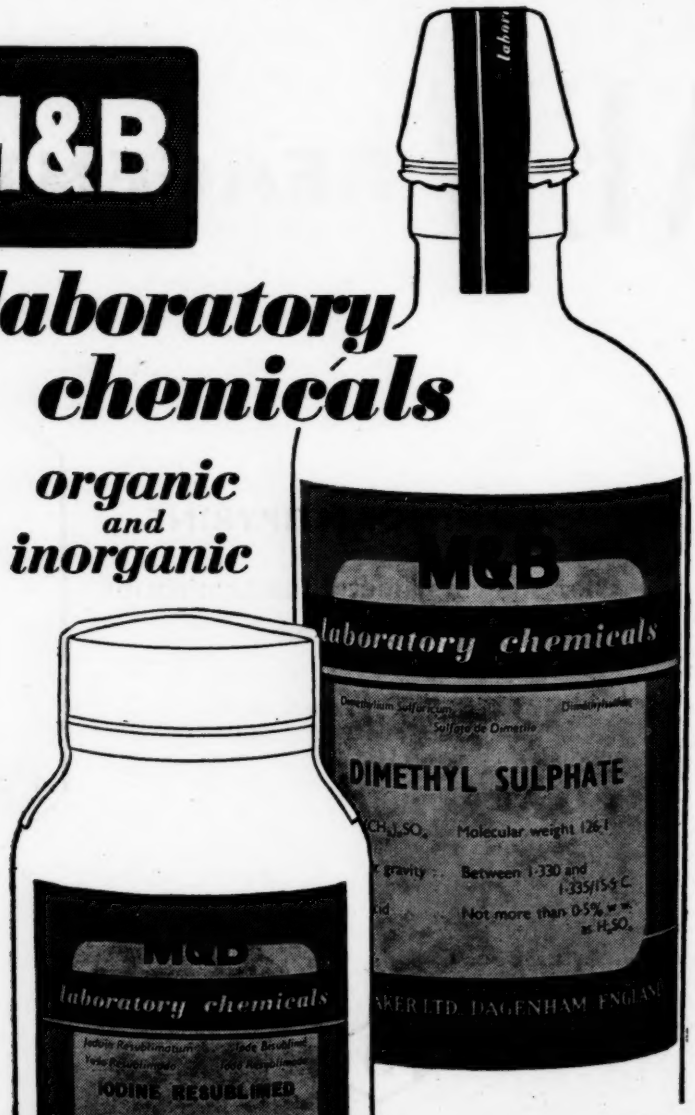

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175. *Carbazoles, Carbolines, and Related Compounds. Part II. Transformations of Some Quaternary Salts of Quindoline.*

By S. J. Holt and V. Petrow.

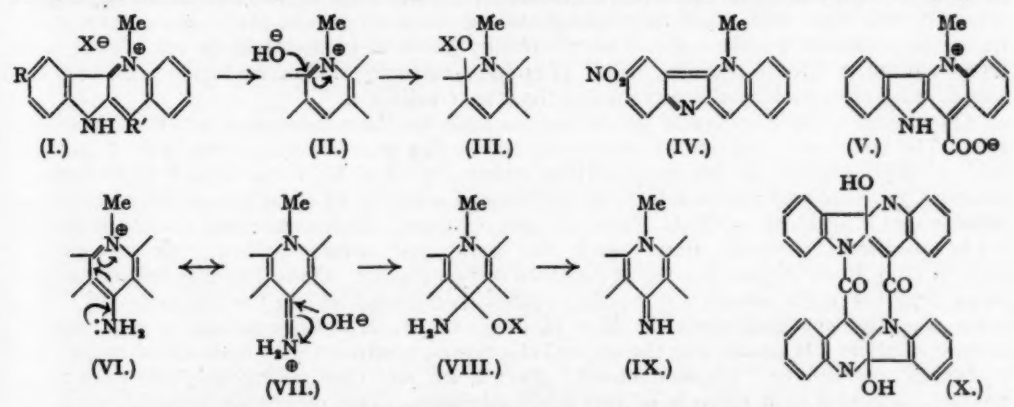
Pseudo-bases of two types have been prepared from quaternary salts of quindoline.

Pseudo-bases of type (III; X = H) are obtained from the quaternary *salts* of quindoline, 7-aminoquindoline, and bisquindolinoyl. These are unchanged by crystallisation from alcohols, and fail to give anhydronium bases. The quaternary *salt* from 7-nitroquindoline (I; R = NO_2, R′ = H, X = Cl), however, by virtue of the activating effect of the 7-nitro-grouping on the pyrrole hydrogen at 10, readily passes into the anhydronium base, *7-nitro-5-methylisoquindoline* (IV), on treatment with alkali.

A pseudo-base of type (VIII; X = H), on the other hand, is obtained from *11-aminoquindoline methiodide* (I; R = H; R′ = NH_2; X = I). In contrast to pseudo-bases of type (III), (VIII; X = H) gives the corresponding *ethers* (VIII; X = Me and Et) on crystallisation from methyl or ethyl alcohol. These pass readily into the *anhydronium base* (IX) by loss of the alcohol.

We have now extended earlier work (Part I; Holt and Petrow, *J.*, 1947, 607) on the relationship between structure and biological activity in the quindoline series, by the preparation of some quaternary salts. Treatment of these with alkali has led to the formation of pseudo-bases, the transformations of which show certain points of interest.

Treatment of 5-methylquindolinium iodide (I; R = R′ = H, X = I) with alkali leads to the formation of a deep violet pseudo-base, readily soluble in chloroform (see Experimental), to which Fichter and Boehringer (*Ber.*, 1906, **39**, 3936; cf. Fichter and Probst, *ibid.*, 1907, **40**, 3478) assigned structure (III; X = H). Their evidence for this formulation rested largely on



the non-formation of a dihydroquindolinone on oxidation. Fichter and Probst (*loc. cit.*) remarked that crystallisation of this base from methyl alcohol failed to produce the corresponding methoxy-compound (III; X = Me), although substitution of hydrogen by alkyl in pseudo-bases by means of this method is a well-established reaction. We have confirmed the evidence submitted by the earlier workers in support of (III; X = H), and have also carried out systematic attempts to convert (III; X = H) into an anhydronium base, but without success. Its formation from (I; R = R′ = H, X = I), it may be added, probably proceeds by the mechanism indicated in (II).

7-Nitroquindoline (Part I, *loc. cit.*), is readily converted into the corresponding *7-nitro-5-methylquindolinium chloride* (I; R = NO_2, R′ = H, X = Cl). In contrast to the methochloride of the parent base (Armit and Robinson, *J.*, 1922, 829), however, this compound passes smoothly into the anhydronium base, *7-nitro-5-methylisoquindoline* (IV) on treatment with alkali in hot methanol. This compound is remarkable for its brilliant scarlet colour, which is not unexpected in view of its interesting and extensive conjugation. Reduction of 7-nitro-5-methylquindolinium chloride (I; R = NO_2, R′ = H, X = Cl) with reduced iron in aqueous alcohol containing a little calcium chloride gave *7-amino-5-methylquindolinium chloride* (I; R = NH_2, R′ = H, X = Cl) which again failed to pass into an anhydronium base, yielding only the pseudo-base (III; R = NH_2, R′ = H, X = H) on treatment with alkali. All operations involving this pseudo-base had to be carried out in an inert atmosphere, as oxidation takes place very readily with formation of an insoluble, green compound. The atypical behaviour of the nitro-quaternary

salt (I; R = NO_2, R′ = H, X = Cl) in forming the anhydronium base (IV) is without doubt a direct result of the activating effect of the polar nitro-grouping on the reactivity of the pyrrole hydrogen atom in position 10.

The behaviour of 11-aminoquindoline (Part I, *loc. cit.*), on the other hand, followed a different pattern. Treatment with methyl iodide in boiling methanol gave *11-amino-5-methylquindolinium iodide* (I; R = H, R′ = NH_2, X = I). The constitution assigned to this compound followed from the observation that 10-acetyl-11-diacetylaminoquindoline (Part I, *loc. cit.*) gave the corresponding *11-amino-5-methylquindolinium chloride* on treatment with methyl sulphate followed by hydrolysis with dilute hydrochloric acid, both the chloride and the iodide obtained by the different routes giving the same alkoxyl pseudo-base and anhydronium base (see below). Treatment of an aqueous suspension of this methochloride with warm dilute ammonium hydroxide, or with cold dilute sodium hydroxide, precipitated a red, insoluble compound converted into the original quaternary salts on treatment with acids. Analytical results were not entirely satisfactory, but this compound is without doubt the corresponding pseudo-base. In striking contrast to compounds of type (III; X = H), however, its crystallisation from methyl or ethyl alcohol gave the respective *11-amino-11-methoxy-* (VIII; X = Me) or *11-amino-11-ethoxy-5-methyl-5 : 11-dihydroquindoline* (VIII; X = Et), passing smoothly on warming by loss of alcohol into the corresponding anhydronium base, *11-imino-5-methyl-5 : 11-dihydroquindoline* (IX). The latter passed into the original methochloride on treatment with hydrochloric acid. The observed experimental results receive a ready interpretation on the basis of formulæ (VIII) and (IX) assigned to the pseudo- and imino-bases. These formulations, too, are readily explicable along the lines indicated in (VI) ⟶ (VII) ⟶ (VIII). A similar rearrangement, it may be added, has been observed by Albert and Ritchie (*J.*, 1943, 459), who obtained 5-imino-10-methylacridane from 5-amino-10-methylacridinium iodide by treatment with alkali followed by heating of the product to 130°. In contrast to the quaternary salt of 5-aminoacridine which readily gives 10-methylacridone on heating with 0·05N-sodium carbonate solution (*ibid.*), 11-amino-5-methylquindolinium iodide gives only the pseudo-base after prolonged heating under the same conditions.

Quindoline-11-carboxylic acid proved too insoluble for direct conversion into the quaternary salt. The latter was prepared by reaction of the readily soluble methyl ester (Part I, *loc. cit.*) with methyl sulphate in benzene solution giving (I; R = H, R′ = CO_2Me, X = $MeSO_4$), followed by hydrolysis with dilute hydrochloric acid whereby *11-carboxy-5-methylquindolinium chloride* (I; R = H, R′ = CO_2H, X = Cl) was obtained. This compound readily dissolved in hot sodium hydroxide from which the garnet-red *sodium* salt of the pseudo-base (III; R = H, R′ = CO_2Na, X = H) crystallised out on cooling. On boiling this compound with water, removal of the elements of sodium hydroxide occurred, giving the *zwitterion* (V). The latter was also obtained when (I; R = H, R′ = CO_2H, X = Cl) was heated with sodium acetate solution. It passed into the original chloride on treatment with hydrochloric acid.

Finally, reaction of " bisquindolinoyl " (Part I, *loc. cit.*) with methyl sulphate gave a red product consisting of a mixture of two methosulphates. This conclusion followed from the results obtained on treating an aqueous solution of the methosulphates with alkali in the presence of chloroform. The red aqueous layer yielded 11-carboxy-5-methylquindolinium chloride (I; R = H, R′ = CO_2H, X = Cl) on treatment with hydrochloric acid. The blue chloroform-soluble fraction gave indigo-blue needles of a compound which was evidently the *pseudo-base* (X), although its analytical figures were not entirely satisfactory.

Experimental.

(M. p.s are corrected. Analyses are by Mr. S. Bance, B.Sc., A.R.I.C., Microanalytical Department, May and Baker Ltd.)

Pseudo-base from 5-Methylquindolinium Chloride (III; X = H).—Improved method of preparation: Chloroform (20 ml.) and 2N-sodium hydroxide (7·5 ml.) were added in turn to 5-methylquindolinium chloride (2·0 g.) (Armit and Robinson, *loc. cit.*), dissolved in warm water (200 ml.), in a separating funnel. After thorough agitation, the chloroform layer was washed, dried, filtered, and evaporated to 5 ml., whereupon dark, reddish-violet needles of the pseudo-base (600 mg.) separated (Found: C, 76·6; H, 5·5; N, 11·1. Calc. for $C_{18}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2%).

7-Nitro-5-methylquindolinium Chloride (I; R = NO_2, R′ = H, X = Cl).—7-Nitroquindoline (2·0 g.) in nitrobenzene (60 ml.) at 150° was treated with methyl sulphate (2·5 ml.). After 1½ hours the product was precipitated with benzene (300 ml.), hydrolysed for 15 mins. with concentrated hydrochloric acid (10 ml.) in methanol (200 ml.; charcoal), and the product which separated on cooling recrystallised from methanol. *7-Nitro-5-methylquindolinium chloride* (1·8 g.; 75%) formed small, bright yellow needles, m. p. 294—296° (decomp.) (Found: N, 13·3; Cl, 11·1. $C_{16}H_{12}O_2N_3Cl$ requires N, 13·4; Cl, 11·3%).

7-Nitro-5-methylisoquindoline (IV), crimson needles from methanol (90 mg.), m. p. 280—283° (Found:

C, 69·3; H, 4·3; N, 15·2. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0; N, 15·2%), was prepared by treating a boiling suspension of 7-nitro-5-methylquindolinium chloride (155 mg.) in methanol (20 ml.) with 2N-sodium hydroxide (0·28 ml.) under reflux for 15 mins.

7-Amino-5-methylquindolinium Chloride (I; R = NH_2, R′ = H, X = Cl).—This *salt*, a yellow, microcrystalline powder (600 mg.) from ethanol–hydrochloric acid (100 : 1, v/v) (Found: N, 14·6; Cl, 12·7. $C_{16}H_{14}N_3Cl$ requires N, 14·8; Cl, 12·5%), was prepared by reducing 7-nitro-5-methylquindolinium chloride (1·25 g.) with reduced iron (3·5 g.) in 80% ethanol (50 ml.) containing calcium chloride (100 mg.) for 12 hours under reflux.

Pseudo-base from 7-Amino-5-methylquindolinium Chloride.—7-Amino-5-methylquindolinium chloride (500 mg.) was dissolved in air-free water (50 ml.) in a separating funnel. Hydrogen was passed through to effect agitation, and freshly distilled chloroform (10 ml.) and air-free 2N-sodium hydroxide (20 ml.) were added in turn. After 5 minutes the chloroform layer was run off into another separating funnel containing air-free water (50 ml.) and a trace of sodium dithionite (hydrosulphite), and agitated by a stream of hydrogen. The washed chloroform layer was dried (Na_2SO_4) in hydrogen and concentrated to *ca.* 2 ml. Indigo-blue needles of the base crystallised out (Found: C, 72·6; H, 5·3; N, 15·9. $C_{16}H_{13}ON_3$ requires C, 72·5; H, 5·7; N, 15·8%).

11-Amino-5-methylquindolinium iodide (I; R = H, R′ = NH_2, X = I), yellow microscopic needles (2·15 g.) from methanol, which decomposed on heating with liberation of iodine (Found: N, 11·3; I, 33·6. $C_{16}H_{14}N_3I$ requires N, 11·2; I, 33·8%), was obtained by heating 11-aminoquindoline (2·4 g.) with methyl iodide (10 ml.) in methanol (25 ml.) under reflux for 4 hours.

11-Amino-5-methylquindolinium Chloride.—Triacetyl-11-aminoquindoline (1·0 g.) in nitrobenzene (20 ml.) at 160° was treated with methyl sulphate (0·4 ml.) for 30 minutes. The product, precipitated with benzene (100 ml.), was heated under reflux with 2N-hydrochloric acid (100 ml.) for 30 minutes, and the solid which separated on cooling recrystallised from methanol. *11-Amino-5-methylquindolinium chloride* (500 mg.) formed yellow micro-needles charring at 375° (Found: N, 14·8; Cl, 12·5. $C_{16}H_{14}N_3Cl$ requires N, 14·8; Cl, 12·5%).

11-Amino-11-ethoxy-5-methyl-5 : 11-dihydroquindoline (VIII; X = Et), reddish-orange needles (150 mg.) from ethanol (Found: C, 73·9; H, 6·4; N, 14·2; OEt, 15·2. $C_{18}H_{19}ON_3$ requires C, 73·8; H, 6·5; N, 14·3; OEt, 15·4%), was prepared by adding 2N-sodium hydroxide (0·55 ml.) to a boiling suspension of 11-amino-5-methylquindolinium iodide (375 mg.) in pure ethanol (10 ml.), heating the mixture under reflux for 5 mins., and allowing the filtered solution to cool.

11-Amino-11-methoxy-5-methyl-5 : 11-dihydroquindoline (VIII; X = Me), prepared as above but using methanol (20 ml.), formed long, orange needles (200 mg.) from methanol (Found: C, 73·4; H, 6·0; N, 15·1; OMe, 10·8. $C_{17}H_{17}ON_3$ requires C, 73·2; H, 6·1; N, 15·1; OMe, 11·1%). On treatment of its methanolic solution (200 mg. in 40 ml.) with concentrated hydrochloric acid (0·2 ml.), 11-amino-5-methylquindolinium chloride separated on standing (Found: N, 14·8; Cl, 12·4%), identical with the product described above.

11-Imino-5-methyl-5 : 11-dihydroquindoline (IX), a vermilion powder or needles decomposing at *ca.* 172° (Found: C, 78·0; H, 5·5; N, 16·9. $C_{16}H_{13}N_3$ requires C, 77·8; H, 5·3; N, 17·0%), was prepared by heating finely powdered analytically pure 11-amino-11-methoxy-5-methyl-5 : 11-dihydroquindoline at 110°/10 mm. for 15 minutes. With acids it gave the corresponding 11-aminoquindoline quaternary salts.

11-Carbomethoxy-5-methylquindoline 5-methosulphate (I; R = H; R′ = CO_2Me, X = $MeSO_4$), red needles (3·2 g.) from methanol, m. p. 274° (decomp.) (Found: C, 56·7; H, 4·6; N, 7·2; OMe, 15·2. $C_{19}H_{18}O_6N_2S$ requires C, 56·7; H, 4·5; N, 7·0; OMe, 15·4%), was prepared by treating a solution of 11-carbomethoxyquindoline (7·0 g.) in benzene (250 ml.) with methyl sulphate (3·6 ml.) under reflux for 5 hours.

11-Carboxy-5-methylquindolinium chloride (I; R = H, R′ = CO_2H, X = Cl), orange needles giving an amorphous red powder (900 mg.) on drying at 100°/10 mm., m. p. 268° (decomp.) (Found: N, 8·8; Cl, 11·6. $C_{17}H_{13}O_2N_3Cl$ requires N, 9·0; Cl, 11·4%), was obtained when an aqueous solution of the foregoing ester (1·5 g.) was heated under reflux with concentrated hydrochloric acid (5 ml.) for 30 minutes and the mixture allowed to cool. The product was very soluble in water, and was washed with 2N-hydrochloric acid and dried over potash in a vacuum.

The sodium salt of the pseudo-base from 11-carboxy-5-methylquindolinium chloride, garnet-red needles (500 mg.) (Found: C, 64·6; H, 4·0; N, 9·0. $C_{17}H_{12}O_2N_3Na$ requires C, 64·5; H, 4·1; N, 8·9%), was obtained when a hot solution of the chloride (500 mg.) in water (10 ml.) was added to hot 2N-sodium hydroxide (10 ml.), and the mixture heated until solution was complete and allowed to cool.

The corresponding *zwitterion* (V) was obtained when (*a*) the foregoing sodium salt (400 mg.) was heated under reflux with water (20 ml.) for 20 minutes and the mixture allowed to cool, m. p. 265° (decomp.) (Found: N, 10·2. $C_{17}H_{13}O_2N_3$ requires N, 10·2%), or (*b*) solid sodium acetate (5·0 g.) was added to a hot solution of 11-carboxy-5-methylquindolinium chloride (1·0 g.) in water (50 ml.). Concentrated hydrochloric acid was then carefully added just to redissolve the flocculent precipitate, followed by a further quantity of sodium acetate (5·0 g.). The hot filtered solution (charcoal) deposited yellow needles of the zwitterion, m. p. 265° (decomp.) (Found: C, 73·9; H, 4·5; N, 10·2. Calc.: C, 73·9; H, 4·4; N, 10·2%), identical with the product obtained under (*a*).

Quaternisation of "Bisquindolinoyl".—Bisquindolinoyl (2·4 g.) in nitrobenzene (50 ml.) was treated at 160° for 1½ hours with methyl sulphate (3 ml.). The red crystalline product (1·8 g.), dissolved in water (150 ml.) in a separating funnel, was treated with chloroform (50 ml.) followed by 2N-sodium hydroxide until alkaline to phenolphthalein. After thorough shaking, the dark blue chloroform layer was separated, the aqueous layer extracted with fresh chloroform (25 ml.), and the combined extracts washed, dried, and concentrated to *ca.* 7·5 ml. under reduced pressure. The product from chloroform (5 ml.) gave lustrous blue-black needles of the *pseudo-base* (X) (500 mg.), m. p. *ca.* 173° (with previous decomp.) (Found on sample dried at 56°/10 mm.: C, 73·6; H, 4·7; N, 9·9. $C_{34}H_{24}O_4N_4$ requires C, 74·1; H, 4·4; N, 10·1%). Acidification of the reddish-purple aqueous layer with hydrochloric acid

gave orange-red needles on standing, identified as 11-carboxy-5-methylquindolinium chloride (400 mg.), m. p. 268° (decomp.), alone or in admixture with an authentic specimen (Found: N, 8·9. Calc. for $C_{17}H_{13}O_2N_2Cl$: N, 9·0%).

Biological Data.—Dr. R. Wien, Biological Division, May and Baker Ltd., has very kindly reported the following results: 7-Amino- and 11-amino-quindolines are inactive as trypanocidal or anti-malarial substances. Of the quaternary salts, only 11-amino-5-methylquindolinium acetate slowed a slight, but not curative, effect against *T. congolense*. Some of the compounds showed greater potentialities as antibacterial agents. Three, namely 11-aminoquindoline, and the 7-nitro- and 11-amino-quindolinium salts, were active *in vitro* against *B. coli* at a dilution of 1 : 128,000. Against *Staph. aureus* they showed fairly high activity in broth. This was reduced in the presence of blood to 1 : 16,000—64,000, except in the case of the 5-methylquindolinium chloride which was active at 1 : 128,000.

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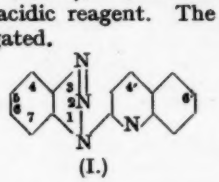
176. *Carbazoles, Carbolines, and Related Compounds. Part III. Quinindoline Derivatives.*

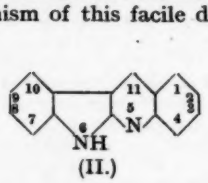
By S. J. HOLT and V. PETROW.

Quinindoline (II), and its 11-*methyl*-, 2-*methoxy*-11-*methyl*-, and 8 : 9-*dimethoxy*-derivatives have been prepared by pyrolytic decomposition of the appropriate 1-α-*quinolylbenztriazoles* (I). 9-*Nitroquinindoline*, obtained by direct nitration of (II), was converted by reduction and acetylation into 6-*acetyl*-9-*diacetylaminoquinindoline*, the constitution of which followed from its alternative preparation from 2′ : 5-*dinitrobenzylideneoxindole*.

The corresponding *quinindolinium* salts (IV) failed to show outstanding biological activity. On treatment with alkali they passed into the *anhydronium bases* (V).

WORK on the relationship between structure and biological activity in the azacarbazole series, initiated in Part I (Holt and Petrow, *J.*, 1947, 607), has now been extended to some derivatives of quinindoline (II). Although this compound may be prepared by the reduction of *oo*′-dinitro-α-cyanodibenzyl (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 3019), or of *o*-nitrobenzylideneoxindole (III; R = H) (Kirchner, *Nachr. K. Ges. Wiss. Göttingen*, 1921, 154), these methods proved unsuitable for our purpose. The required derivatives were obtained by the extension of the Graebe–Ullmann carbazole synthesis first described by Lawson, Perkin, and Robinson (*J.*, 1924, 627), whereby 1-α-quinolylbenztriazoles (I) are pyrolytically decomposed to give the quinindoline and nitrogen. Study of this reaction has now shown that pyrolytic decomposition of the triazoles (I) fails to occur in neutral or basic media such as nitrobenzene, quinoline, and liquid paraffin at their boiling points. In striking contrast, smooth decomposition at 170° takes place in syrupy phosphoric acid, a reagent first introduced for this purpose by Robinson and Thornley (*J.*, 1924, 2169), *i.e.*, under very much less drastic conditions than those obtaining in the absence of the acidic reagent. The mechanism of this facile decomposition in acidic media is being investigated.


(I.)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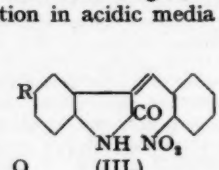
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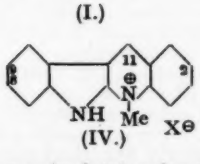
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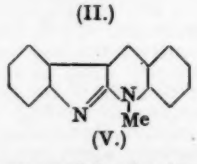
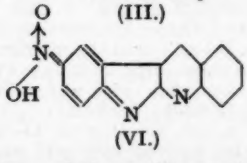

(V.)


(VI.)

The required triazoles (I) were prepared by heating a mixture of the α-chloroquinoline, a slight excess of *o*-phenylenediamine, copper powder, and a little hydrochloric acid under reduced pressure, a procedure which gave somewhat improved yields, followed by treatment of the product with nitrous acid. 1-α-*Lepidylbenztriazole* and 1-α-(6′-*methoxylepidyl*)*benztriazole* were prepared in this way. 4 : 5-Diaminoveratrole and α-chloroquinoline gave 5 : 6-*dimethoxy*-1-α-*quinolylbenztriazole*. An attempt to prepare 8-nitrolepidyl-*o*-phenylenediamine by fusion of 2-chloro-8-nitrolepidine with *o*-phenylenediamine resulted in an explosion. Attempts to prepare 1-α-(4′-carboxyquinolyl)benztriazole from 2-chlorocinchoninic acid and *o*-phenylenediamine were unsuccessful, reaction only occurring at temperatures at which concomitant decarboxylation took place, so that treatment with nitrous acid led to the formation of (II).

Decomposition of these triazoles in syrupy phosphoric acid gave quinindoline (II) and its 11-*methyl*-, 2-*methoxy*-11-*methyl*-, and 8 : 9-*dimethoxy*-derivatives.

Nitration of quinindoline to a mononitro-derivative had previously been carried out by Graebe and Eschenbach (*loc. cit.*), who failed to orient their product. As indole derivatives generally nitrate *para* to the pyrrole nitrogen (cf. quindoline ⟶ 7-nitroquindoline, Part I, *loc. cit.*), we assigned the constitution of a 9-*nitroquinindoline* to this product, a formulation confirmed by its reduction and acetylation to 6-*acetyl*-9-*diacetylaminoquinindoline*, identical with an authentic specimen. The latter was prepared by an extension of Kirchner's quinindoline synthesis (*loc. cit.*) by fusion of 5-nitro-oxindole (Sumpter, Miller, and Magan, *J. Amer. Chem. Soc.*, 1945, **67**, 499) with *o*-nitrobenzaldehyde to give 2′ : 5-*dinitrobenzylideneoxindole* (III; R = NO_2), followed by catalytic reduction and acetylation.

Conversion of some of the above derivatives into the quaternary salts (IV) gave 5-*methyl*-, 5 : 11-*dimethyl*-, 2-*methoxy*-5 : 11-*dimethyl*-, and 9-*nitro*-5-*methyl*-*quinindolinium chloride*. Treatment of these with alkali gave the corresponding anhydronium bases (V) : 5-*methyl*-, 5 : 11-*dimethyl*-, 2-*methoxy*-5 : 11-*dimethyl*-, and 9-*nitro*-5-*methyl*-iso*quinindoline*. These regenerated the quinindolinium salts (IV) on treatment with acids, and were used in the preparation of the soluble methoacetates (IV; X = OAc) employed for biological testing (see Experimental), the methochlorides proving too insoluble for this purpose. Attempts to condense 5 : 11-*dimethylquinindolinium iodide* with *p*-dimethylaminobenzaldehyde to the styryl derivative by Petrow's method (*J.* 1945, 18) were not successful, probably owing to the very sparing solubility of the quaternary salt. There was evidence of reaction, however, as indicated by the appearance of a deep red coloration.

Treatment of an aqueous-alcoholic solution of 9-nitroquinindoline with sodium hydroxide gave a bright reddish-orange solution. This coloration is certainly due to the formation of the sodium salt of the ψ-nitrolic acid (VI). In contrast, the corresponding anhydronium base, 9-nitro-5-methyl*iso*quinindoline, which *a priori* cannot undergo prototropic change to a ψ-nitrolic acid, fails to give a coloration with alkali.

Experimental.

(M. p.s are corrected; semimicroanalyses are by Mr. S. Bance, B.Sc., A.R.I.C., Microanalytical Dept., May and Baker Ltd.).

1-α-*Quinolylbenztriazole.*—α-Chloroquinoline (16·36 g.), *o*-phenylenediamine (12 g.), copper powder (0·5 g.), and concentrated hydrochloric acid (2 drops) were mixed in a flask fitted with a reflux air-condenser, the top of which was connected to a water-pump. The mixture was heated at 155°/30 mm. for 30 mins., and the product dissolved in alcohol (200 ml.), filtered, and added to 2N-hydrochloric acid (250 ml.). The resulting solution was cooled to 0°, and then slowly added to a solution of sodium nitrite (25 g.) in water (200 ml.) at 0° with mechanical stirring. After 30 minutes the precipitate was collected, washed with water, and crystallised from ethanol. 1-α-Quinolylbenztriazole formed faintly-coloured needles, (16 g., 65%), m. p. 145—146° (Found : N, 22·9. Calc. for $C_{15}H_{10}N_4$: N, 22·9%).

1-α-*Lepidylbenztriazole* was prepared from 2-chlorolepidine (*Org. Synth.*, **24**, p. 28). It separated from alcohol as a cotton-wool-like mass which changed, on standing overnight in contact with the solvent, into stout, white needles, m. p. 164—165° (Found : C, 73·7; H, 4·8; N, 21·9. $C_{16}H_{12}N_4$ requires C, 73·8; H, 4·7; N, 21·5%). Yield, 58%.

1-α-(6-*Methoxylepidyl*)*benztriazole*, prepared from 2-chloro-6-methoxylepidine (Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 84), formed pale yellow plates (51%) from acetic acid, m. p. 162—163° (Found : C, 70·1; H, 4·9; N, 19·2. $C_{17}H_{14}ON_4$ requires C, 70·3; H, 4·8; N, 19·3%).

5 : 6-*Dimethoxy*-1-α-*quinolylbenztriazole*, prepared from 4 : 5-diaminoveratrole, formed pale buff-coloured needles (27%) from alcohol, m. p. 193—194° (Found : C, 66·5; H, 4·7; N, 18·3. $C_{17}H_{14}O_2N_4$ requires C, 66·6; H, 4·6; N, 18·3%).

Quinindoline.—1-α-Quinolylbenztriazole (15 g.) in syrupy phosphoric acid (150 ml.) was heated to 150°. When the brisk evolution of gas had slackened, the dark solution was heated to 180° for one minute, cooled, and poured on crushed ice (500 g.). The yellow solid was collected, basified by warming with 2N-ammonium hydroxide, and crystallised from pyridine. Quinindoline formed flat, pale yellow needles (36%), m. p. 346° (Found : C, 82·6; H, 4·6; N, 12·8. Calc. for $C_{15}H_{10}N_2$: C, 82·6; H, 4·5; N, 12·9%).

11-*Methylquinindoline*, prepared from 1-α-lepidylbenztriazole, formed faintly yellow needles (26%) from pyridine, m. p. 274—275° (Found : C, 82·6; H, 5·1; N, 12·2. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%). Its 6-*acetyl* derivative, prepared by heating the base with acetic anhydride for ten minutes under reflux, formed fine white needles from alcohol, m. p. 171·5—172° (Found : N, 10·2. $C_{18}H_{14}ON_2$ requires N, 10·2%).

2-*Methoxy*-11-*methylquinindoline*, prepared from 1-α-(6-methoxylepidyl)benztriazole, formed pale yellow needles (24%) from pyridine, m. p. 305—307° (Found : C, 77·7; H, 5·3; N, 10·6. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%). The 6-*acetyl* derivative formed flat needles from acetic anhydride, m. p. 182—183° (Found : N, 9·2. $C_{19}H_{16}O_2N_2$ requires N, 9·2%).

8 : 9-*Dimethoxyquinindoline*, prepared from 5 : 6-dimethoxy-1-α-quinolylbenztriazole, formed light lemon-yellow needles (4%) from ethanol, m. p. 277—278° (Found : C, 73·2; H, 5·1; N, 10·2. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%). The 6-*acetyl* derivative formed pale yellow needles from acetic anhydride, m. p. 183—184° (Found : N, 8·8. $C_{19}H_{16}O_2N_2$ requires N, 8·8%).

9-Nitroquinindoline.—Quinindoline (2·0 g.) was heated with nitric acid (20 ml., *d* 1·42) until solution was complete. After standing overnight at room temperature, the product was poured into water, the solids collected, basified by warming with N-ammonium hydroxide, and crystallised from glacial acetic acid. *9-Nitroquinindolinium acetate* formed yellow needles (1·96 g.) (Found: loss in wt. on drying, 18·5. $C_{15}H_9O_2N_3,CH_3{\cdot}CO_2H$ requires $CH_3{\cdot}CO_2H$, 18·6%), which lost acetic acid on heating to give 9-nitroquinindoline, m. p. 377—378° (Found: C, 68·4; H, 3·5; N, 16·0. Calc. for $C_{15}H_9O_2N_3$: C, 68·5; H, 3·4; N, 16·0%).

9-Aminoquinindoline.—9-Nitroquinindoline (2·63 g.), reduced iron (10·0 g.), calcium chloride (200 mg.), and 70% alcohol (100 ml.) were heated under reflux for 72 hours, and the mixture filtered hot. The iron residues contained some yellow crystalline material which was extracted with alcohol (Soxhlet). The bulked filtrates yielded *9-aminoquindoline* (45%), which formed a microcrystalline yellow powder from butanol (Found, in dried sample: C, 77·1; H, 4·5; N, 17·9. $C_{15}H_{11}N_3$ requires C, 77·2; H, 4·8; N, 18·0%). The 6 : 9 : 9-*triacetyl* derivative formed small needles from alcohol, m. p. 223·5—224·5° (Found: C, 70·2; H, 4·9; N, 11·8. $C_{21}H_{17}O_3N_3$ requires C, 70·3; H, 4·7; N, 11·7%).

2′ : 5-Dinitrobenzylideneoxindole (III).—A mixture of 5-nitro-oxindole (2·65 g.) (Sumpter, Miller, and Magan, *loc. cit.*) and *o*-nitrobenzaldehyde (2·5 g.) was heated at 170° for 15 minutes, reaction then having occurred and the mass become solid. The product, from chlorobenzene, gave *2′ : 5-dinitrobenzylideneoxindole*, yellow needles (57%) from alcohol, m. p. 253—254° (Found: C, 57·7; H, 3·1; N, 13·3. $C_{15}H_9O_5N_3$ requires C, 57·8; H, 2·9; N, 13·5%). Catalytic reduction of this product in glacial acetic acid in the presence of 10% palladised charcoal, followed by acetylation with acetic anhydride, gave 6-acetyl-9-diacetylaminoquinindoline, m. p. 223·5—224·5° (Found: C, 70·2; H, 4·8; N, 11·8%), not depressed in admixture with a sample prepared from the nitroquinindoline (above).

5-Methylquinindolinium Chloride.—Quinindoline (2 g.) in dry nitrobenzene (50 ml.) was heated with methyl sulphate (2·5 ml.) at 160° for one hour. The cooled product was added to dry benzene (250 ml.). The crude methosulphate, collected after one hour, was dissolved in hot water (100 ml.), and the filtered solution (charcoal) treated with concentrated hydrochloric acid (5 ml.). Light yellow needles of *5-methylquinindolinium chloride* (2·1 g.) separated on cooling, m. p. 278—280° (decomp.) (Found on dried sample: C, 71·4; H, 4·6; N, 10·4; Cl, 13·1. $C_{16}H_{12}N_2Cl$ requires C, 71·5; H, 4·8; N, 10·4; Cl, 13·2%).

5-Methylisoquinindoline, orange-yellow needles from a large bulk of hot water, m. p. 108—110° (Found: C, 82·4; H, 5·2; N, 12·0. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%), was precipitated when the foregoing chloride (1·0 g.), dissolved in hot water at 60°, was treated with 2N-sodium hydroxide solution until the mixture was alkaline to phenolphthalein.

5 : 11-Dimethylquinindolinium iodide, prepared *via* the methosulphate, formed orange needles from water, m. p. 288—289° (Found: C, 54·5; H, 4·1; N, 7·4; I, 33·6. $C_{17}H_{15}N_2I$ requires C, 54·6; H, 4·0; N, 7·5; I, 33·9%). The *methochloride* formed pale yellow needles, m. p. 280—282° (Found: C, 72·2; H, 5·2; N, 9·8; Cl, 12·4. $C_{17}H_{15}N_2Cl$ requires C, 72·2; H, 5·3; N, 9·9; Cl, 12·6%).

5 : 11-Dimethylisoquinindoline formed orange-yellow needles from 50% ethanol, m. p. 218—219° (Found: C, 82·7; H, 5·6; N, 11·3. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

2-Methoxy-5 : 11-dimethylquinindolinium chloride, prepared *via* the methosulphate, formed small plates from N-hydrochloric acid, m. p. 272—274° (decomp.) (Found: C, 69·1; H, 5·6; N, 8·8; Cl, 11·2. $C_{18}H_{17}ON_2Cl$ requires C, 69·2; H, 5·5; N, 8·9; Cl, 11·4%).

2-Methoxy-5 : 11-dimethylisoquinindoline formed orange micro-needles from water, m. p. 159—160° (Found: C, 78·1; H, 5·6; N, 10·2. $C_{18}H_{16}ON_2$ requires C, 78·2; H, 5·8; N, 10·1%).

9-Nitro-5-methylquinindolinium chloride, prepared *via* the methosulphate, separated from dilute hydrochloric acid as a microcrystalline, yellow solid, m. p. 295—300° (decomp.) (Found: C, 61·2; H, 3·7; N, 13·3; Cl, 11·1. $C_{16}H_{12}O_2N_3Cl$ requires C, 61·3; H, 3·9; N, 13·4; Cl, 11·3%).

9-Nitro-5-methylisoquinindoline formed orange needles from a large volume of alcohol, m. p. 262° (Found: C, 69·5; H, 3·9; N, 15·0. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0; N, 15·2%).

Biological Data.—Dr. R. Wien, Biological Division, May and Baker Ltd., has very kindly reported the following results: The quaternary salts were inactive against *T. equiperdum* and *T. congolense* with the exception of 5 : 11-dimethylquinindolinium acetate, which showed a slight, but no curative, effect against the latter organism. 5 : 11-Dimethyl-, and 2-methoxy-5 : 11-dimethyl-quinindolinium acetates were active *in vitro* against *Staph. aureus* in broth at dilutions of 1 : 128,000 and 1 : 256,000, but the activity fell to 1 : 16,000 and $<$1 : 8000 in the presence of blood. Activity against *B. coli* and *Ps. pyocyanea* was not appreciable.

The authors thank Dr. A. J. Ewins, D.Sc., F.R.S., and the Directors of Messrs. May and Baker Ltd., for research facilities generously placed at the disposal of one of them (S. J. H.) for the work described in this and the preceding paper.

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177. *The Amylolytic Degradation of Starch. A Revision of the Hypothesis of Sensitisation.*

By E. J. BOURNE, SIR NORMAN HAWORTH, A. MACEY, and S. PEAT.

An extension of the work of Haworth, Kitchen, and Peat (1943) on the amylolysis of starch has provided data which necessitate a revision of the tentative hypothesis then advanced to account for the "sensitisation" of the limit dextrin-A by the action of salivary amylase. Dextrin-A is resistant to the hydrolytic action of β-amylase until it is "sensitised" by contact

with salivary α-amylase. To explain this effect the suggestion was made that the function of the α-amylase in sensitisation was the scission and resynthesis of the 1 : 6-glucosidic linkages constituting the cross (or polymeric) links in the branched structure of dextrin-A (and of amylopectin from which it is derived).

The experimental results described in this communication cannot be reconciled with the suggested mode of action of α-amylase but are explicable in terms of the conception of α-amylolysis as being the hydrolytic scission of the normal 1 : 4-glucosidic bonds of " inner " chains (an inner chain is a chain of 1 : 4-linked α-glucose members situated between two branch points). Contrary to our earlier view it would seem that the cross linkages of branched structures like amylopectin are resistant to hydrolysis by α-amylase.

Sufficient information is not yet available to enable a decision to be reached on the molecular constitution of ramified structures such as amylopectin. The properties of amylopectin can be equally well interpreted in terms of the branched or laminated formulation of Haworth and Hirst which was the simplest expression capable of illustrating the facts then available, or by an extension of this idea in which more than one cross linking is introduced. The extreme case is illustrated by the formulation by K. H. Meyer of an irregular model with multiple branching of chains.

Some comments are made on Myrbäck's hypothesis concerning the biogenesis of starch.

In 1943, Haworth, Kitchen, and Peat (*J.*, 1943, 619) recorded some observations on the degradation of starch by amylolytic action to account for which a hypothesis was provisionally advanced concerning the mechanism of the action of α-amylase on starch. The facts were briefly as follows : (i) the hydrolysis of starch by β-amylase proceeded until 60% of the starch had been converted into maltose; (ii) the remaining 40% consisted of a limit dextrin (dextrin-A) which was resistant to the further action of β-amylase; (iii) when dextrin-A was submitted to the action of salivary amylase, the dextrin was " sensitised " in the sense that it was once more susceptible to the hydrolytic action of β-amylase, by the agency of which it was converted into maltose (40%) and a second limit dextrin (dextrin-B, 60%); (iv) the sensitisation of dextrin-A appeared to be effected by a very brief contact with salivary amylase (the α-amylase was in each experiment destroyed by boiling before the β-amylase was added) and to be accomplished without the liberation of reducing groups.

It appeared possible at that time to accommodate these facts on the view that the points of junction of the repeating unit chains of the branched component of starch (amylopectin) constituted obstructions to the end-wise attack of β-amylase, the action of which on amylopectin ceased when the branch points were reached. The sensitising action of salivary amylase was then conceived as a removal of the obstructions by scission of the glucosidic linkages (believed to be 1 : 6-linkages) constituting the branch points. To account for the fact that the sensitised dextrin-A did not behave towards β-amylase as if it consisted entirely of unbranched chains of the amylose type, it was necessary to assume either that the salivary amylase attacked only a selected number of the 1 : 6-cross linkages or that the scission of 1 : 6-linkages by this enzyme was a reversible reaction and that the polymeric or cross linkage between two unit-chains was reconstituted in a different position. Of the alternative hypotheses, the latter was preferred for reasons given in the paper cited.

The experimental work described in the 1943 paper was actually carried out much earlier and was recorded in thesis form in 1937. Great advances have been made during the past decade in the technique of starch analysis and in the investigation of amylase reactions, and the purpose of this communication is to describe the results of the application of these more refined methods to the study of the problem outlined above. The observations of Haworth, Kitchen, and Peat have been for the most part confirmed and extended, but in one essential particular we have now found that the chosen methods of sugar analysis used earlier were not sufficiently precise for the purpose and led to the erroneous conclusion that the sensitisation of dextrin-A occurred without the concomitant liberation of reducing groups.

The chief refinements introduced in the present work consisted in (*a*) the use of a β-amylase preparation from soya bean which was shown to be free from contamination by α-amylase and maltase; (*b*) the preparation of dextrin-A under rigidly controlled conditions by the action of the soya bean β-amylase on an amylopectin separated from potato starch by the thymol method (Haworth, Peat, and Sagrott, *Nature*, 1946, **157**, 19); (*c*) the use of copper reagents (Shaffer–Hartmann and Somogyi) adapted to a semi-micro-scale, to estimate the extent of hydrolysis effected at any stage in a digestion; (*d*) the quantitative determination of the iodine-staining power of a digest (the Absorption Value, A.V.) and the diminution of this value [expressed as a percentage of the Blue Value (B.V.) of the original dextrin-A], as hydrolysis proceeded; and (*e*) a strict quantitative control of enzyme concentration and of the reaction time.

The β-amylase was used throughout these experiments in such concentration that, while it effected a rapid hydrolysis of amylose, its action on the dextrin-A was negligibly small. The

effectiveness of the action of salivary amylase was varied by changing either the concentration or the time of action of this enzyme.

The observations made on the sensitisation of dextrin-A are summarised in the Table, and some of these results are given graphical expression in the Figure.

The Successive Actions of α- and β-Amylase on Dextrin-A.

Digest.	Dilution of stock solution of salivary α-amylase (×).	Duration of action of α-amylase (mins.).	Iodine colour (% diminution of A.V. after α-amylase action) (6800 A.).	% Apparent conversion into maltose effected by: α-Amylase alone.	α-Amylase followed by β-amylase (total).	β-Amylase (alone) after sensitisation (difference).
1	10,000	*ca.* 0·5	0	0	0	0
2	1000	,,	0	0	0	0
3	100	,,	0	0	0	0
4	100	,,	1·1	0	0	0
5	50	,,	12·1	—	10·45	—
6	50	,,	12·9	—	11·8	—
7	20	,,	54·2	—	21·4	—
8	20	,,	48·7	—	18·6	—
9	10	,,	88·5	11·75	28·2	16·45
10	10	,,	84·6	15·1	32·4	17·3
11	500	5	0	0	0	0
12	200	5	2·7	—	10·4	—
13	500	15	2·1	—	—	0
14	100	5	23·0	—	13·5	—
15	200	15	17·6	—	12·5	—
16	50	5	67·0	8·7	21·9	13·2
17	100	10	51·1	5·3	16·35	11·05
18	100	15	52·2	—	19·1	—
19	200	30	47·8	6·1	19·2	13·1
20	100	20	75·6	12·5	26·8	14·3
21	50	15	90·5	16·7	30·2	13·5
22	20	15	Achroic	37·5	44·1	6·6
23	10	15	,,	41·0	46·6	5·6
24	5	15	,,	47·5	51·9	4·4
25	1	15	,,	52·8	58·3	5·5
26	1	30	,,	57·7	62·2	4·5
27	1	60	,,	—	67·3	—
28	1	60	,,	63·3	70·5	7·2
29	1	120	,,	71·4	74·3	2·9
30	200	5	23·5	2·1	14·7	12·6
31	200	10	34·0	2·9	15·6	12·7
32	200	15	54·5	5·7	18·9	13·2
33	50	0·5	49·5	4·45	—	—

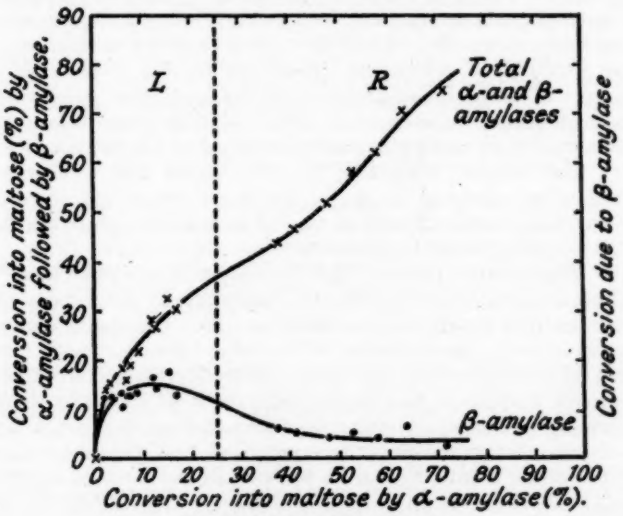
It is at once apparent that an essential step in the sensitisation of dextrin-A by the action of α-amylase is the hydrolytic fission of some of the glucosidic linkages. When the concentration and time of action of the salivary amylase are so ordered that no diminution of A.V. or increase in reducing power of the digest is observed, then no sensitisation of the dextrin-A occurs. Otherwise expressed, some degree of hydrolysis of dextrin-A by the sensitising enzyme is an essential prerequisite for its further hydrolysis by β-amylase.

If sensitisation connotes hydrolysis and total resynthesis of cross-linkages, no liberation of reducing groups would occur during the process, and this is contrary to the experimental facts. If it be supposed that the action of α-amylase is purely hydrolytic and is confined to the scission of 1 : 6-linkages, it can be calculated, on the basis of a unit-chain length of 12 glucose members (Haworth, Hirst, Kitchen, and Peat, *J.*, 1937, 791), that dextrin-A would yield a mixture of unbranched dextrins the reducing power of which would be approximately one-sixth of that of maltose, *i.e.*, the scission (without resynthesis) of all the 1 : 6-links in dextrin-A would be accompanied by an increase in reducing power corresponding to an apparent conversion into maltose of about 17%. It is now shown that this supposition also is not in keeping with the known facts. Thus, the scission of all the cross-linkages in dextrin-A would remove all the postulated obstructions to β-amylase hydrolysis, and the subsequent action of this enzyme on the sensitised dextrin would be expected to lead to complete, or nearly complete, conversion into maltose. The results given graphically in the Figure (region L) show quite clearly that this is not so. The action of β-amylase on an α-amylase-treated digest, having a reducing value

corresponding to 17% apparent conversion into maltose, ceases when the total conversion figure reaches 30—32%. In other words, β-amylase is able to effect a further conversion of 13—15% only, instead of the 80% expected if the above postulate were true.

Finally, if sensitisation consists in the hydrolysis of a proportion only of the 1 : 6-linkages, then as the percentage apparent conversion into maltose by α-amylase increases, the subsequent percentage conversion by β-amylase should increase also, as the obstructing branch points are progressively removed. Again, this is contrary to the facts. The graph shows that, as the percentage conversion by α-amylase was increased from 2 to 18%, the subsequent action of β-amylase further degraded the sensitised dextrin-A by an amount which was approximately the same (13% conversion into maltose) for each specimen.

When the results of the prolonged exposure of dextrin-A to the sensitising action of α-amylase are examined (Region R in the Figure), the persistence of 1 : 6-linkages is even more strikingly indicated. In this series of experiments, the greater part of the degradation of dextrin-A was effected by the agency of the α-amylase and obviously involved the scission of 1 : 4-links. The activity of the enzyme was sufficiently high to yield products giving no colour with iodine (100% diminution of B.V.). The subsequent action of β-amylase on these achroic dextrins led



Sensitisation of Dextrin-A.

to further hydrolysis, but a limiting factor was still present, and 100% conversion into maltose was never observed, even when three-quarters of the dextrin-A had been initially hydrolysed by α-amylase.

It would seem that these diverse observations can be correlated only on the view that α-amylase, equally with β-amylase, is unable to resolve the polymeric linkages, and that the hydrolytic activity of both amylases is confined to the chain-forming 1 : 4-glucosidic linkages.

The tentative proposal advanced to explain the observations of Haworth, Kitchen, and Peat is thus shown to be inadequate by the further investigation of the phenomenon of sensitisation described in this communication. The branch points (*i.e.*, the polymeric 1 : 6-linkages) which obstruct the action of β-amylase are not hydrolysed in the initial sensitising period of α-amylolysis but persist in the dextrins formed during that period (these dextrins are described as α-dextrins by Myrbäck). No occasion arises, therefore, to postulate a re-synthesis of 1 : 6-linkages as an integral part of the sensitising action.

The sensitisation of dextrin-A is, in fact, explicable in terms of the liberation (by α-amylase scission of 1 : 4-linkages) of new " outer " chains with non-reducing terminal groups. These " outer " chains are susceptible to endwise attack by β-amylase, the action of which proceeds, with the separation of maltose units, until a branch-point is again reached.

Our hypothesis of sensitisation has been criticised by K. Myrbäck (Svedberg Anniversary Volume, 1944, pp. 474—483) as not being in line with the general conception of the course of α-amylolysis. In the light of the results of the further studies described above, we acknowledge the soundness of this criticism and recognise that sensitisation is explicable as being the result of

the scission by α-amylase of some of the 1 : 4-linkages constituting " inner " chains (an inner chain being a chain of 1 : 4-linked α-glucose members situated between two branch points).

While agreeing with Myrbäck's views on the mode of action of α-amylase on starch and its components, we are not yet convinced that the properties of amylopectin (and of the dextrin-A derived from it) are better explained by the irregular, highly ramified structure proposed by K. H. Meyer and Bernfeld (*Helv. Chim. Acta*, 1940, **23**, 880) than by a simpler laminated formulation of which that originally proposed by Haworth, Hirst, and Isherwood (*J.*, 1937, 577) is an example. Myrbäck prefers the Meyer formulation of amylopectin and bases his preference on certain assumptions with regard to the mode of synthesis of starch in the plant. This author states (*loc. cit.*) that " in a certain plant under certain conditions, the probability of attachment of a new glucose unit in the position 6 (which means ramification of the chain) is in constant ratio with the probability of attachment in the position 4 (which means lengthening of the chain). Assuming that γ is the ratio between these probabilities, it is possible to calculate the probable constitution of the molecules formed when synthesis has proceeded for some time ".

We have some reason to believe, however, that the synthesis of amylopectin in the plant does not consist entirely in the building up of chains by the apposition of single glucose units. Studies of the biogenesis of starch in the potato indicate that two enzymes are operative in the synthesis of the branched chain component. The one, P-enzyme or phosphorylase, builds up from glucose-1 phosphate short-chain dextrins (*pseudo*amylose) consisting, on an average, of 20 glucose members joined by 1 : 4-linkages; the other enzyme, Q-enzyme, effects the mutual union by 1 : 6-linkages of these *pseudo*amylose chains and thus gives rise to the branched structure of amylopectin (Bourne and Peat, *J.*, 1945, 877; Bourne, Macey, and Peat, *J.*, 1945, 882). Q-enzyme is incapable of using glucose-1 phosphate as a substrate.

Cori and Cori (*J. Biol. Chem.*, 1943, **151**, 57) have shown that a " cross-linking " enzyme similar to Q-enzyme is an essential factor in the synthesis of glycogen in animal tissues. This factor, like Q-enzyme, functions only in conjunction with a phosphorylase (a P-enzyme). It exerts no action, *per se*, on glucose-1 phosphate.

Furthermore, the presence of a polysaccharide catalyst is necessary as a " starter " even in the synthesis of unbranched chains from glucose-1 phosphate by the agency of P-enzyme. The catalyst appears to constitute a pattern or nucleus on which the chains being synthesised grow by the addition of glucose units, one at a time.

It is not proposed, at present, to amplify or to criticise Myrbäck's hypothesis of the course of α-amylolysis. The main purpose of this communication is to state our revised view that the sensitisation of dextrin-A by α-amylase cannot be divorced from the normal hydrolytic function of α-amylase, this normal function being the scission of 1 : 4-glucosidic linkages. The cross linkages, constituting branch points, appear to be resistant to the hydrolytic activity not only of β-amylase but also of the α-amylase of saliva, and these 1 : 6-glucosidic linkages persist in the dextrins produced by the action on amylopectin of either enzyme.

Experimental.

α-Amylase from Saliva.—A stock solution of salivary α-amylase was prepared by diluting early-morning saliva with an equal volume of water and removing the precipitate of mucin by the centrifuge. Maltase was shown to be absent by incubation with maltose, no increase in reducing power being detected by the Shaffer–Hartmann method. When used in digests containing dextrin-A as substrate, this stock enzyme solution was suitably diluted with water, the greatest dilution being 10^4-fold.

β-Amylase from Soya Bean.—Soya bean was chosen as the source of β-amylase because it had been claimed that the enzyme product, in contrast to that from wheat and barley, was free from contamination by α-amylase. The method of isolation has already been reported (Bourne, Macey, and Peat, *loc. cit.*). The earlier observation that there was no maltase impurity in the product was confirmed.

Estimation of Reducing Sugar.—For the estimation of reducing sugars produced by amylolysis two copper reagents were employed, namely those of Shaffer and Hartmann (*J. Biol. Chem.*, 1921, **45**, 377) and Somogyi (*J. Biol. Chem.*, 1937, **117**, 771). In each case the amount of maltose produced in a digest was estimated from a linear calibration graph (maltose *v.* equivalent volume of thiosulphate solution), which had been obtained by using standard solutions of pure maltose.

The Shaffer–Hartmann reagent, which was stable for periods of at least 4 weeks, was satisfactory for the estimation of 0·4—3·0 mg. of maltose in 5 c.c. of solution, and, of course, more concentrated sugar solutions could be suitably diluted. However, it failed completely to detect smaller amounts of the sugar, *i.e.*, the calibration graph intercepted the axis at about 0·4 mg. owing to re-oxidation of the cuprous oxide by atmospheric oxygen (Somogyi, *loc. cit.*). When it became necessary to measure momentary actions of amylolytic enzymes the method was no longer adequate, without modification, to estimate the traces of maltose thus produced. In such a case a known amount of maltose was incorporated in the digest, and the increase in sugar was then a measure of the extent of amylolysis.

On grounds of convenience this modified procedure was subsequently replaced by the method of Somogyi the use of which enabled maltose concentrations of 0·02—0·90 mg./5 c.c. to be measured. The

copper reagent, which had been specially designed for this purpose, contained sodium sulphate (20%) to reduce the solubility of atmospheric oxygen, and consequently the calibration graph passed through the origin. When the reagent was stored for more than a few days it was apparent that some change had occurred, necessitating a second calibration. Therefore all determinations by the Somogyi method were made as soon as possible after the standardisation.

Measurement of Absorption Value (A.V.).—The expression A.V. is used to describe the reading on the logarithmic scale of a Spekker Photoelectric Absorptiometer when the absorption of light by a solution of a polysaccharide–iodine complex, contained in 4 cm. cells, was measured. The light filters employed were of the Ilford gelatin type (Nos. 601—608, transmitting light of 4300—6800 A.). The wave-length of the light used is stated whenever an absorption value is quoted, *e.g.*, A.V., 0·21 (6800 A.). No stipulation is made with regard to the absolute or relative concentrations of polysaccharide and iodine; indeed in some cases, for example during the course of an amylolytic digest, these are not known.

Measurement of Blue Value (B.V.).—The blue value (B.V.) of a polysaccharide has a special significance; it is the A.V. observed when a polysaccharide is stained with iodine under the standard conditions prescribed by Hassid and McCready (*J. Amer. Chem. Soc.*, 1943, **65**, 1154) and when Ilford gelatin light filters, transmitting light of 6800 A., are employed. Under these conditions the coloured solution contains the polysaccharide (1 mg./100 c.c.), iodine (2 mg./100 c.c.) and potassium iodide (20 mg./100 c.c.). Thus the blue value, in contrast to an absorption value, is characteristic for a given polysaccharide. Since the concentration of the actual coloured material, *i.e.*, the polysaccharide–iodine complex, cannot be readily ascertained, there is no point in evaluating a hypothetical extinction coefficient which, in any case, would be proportional to the blue value.

Although Hassid and McCready (*loc. cit.*) stated that polysaccharide–iodine colours developed to their full intensity almost immediately, we have found that for some polysaccharides, especially for those staining red, this was not quite true. As a precautionary measure, therefore, the coloured solutions were allowed to stand for several hours before the blue value was ascertained. The statement by the same authors that the colours were stable for several days was verified.

Preparation of Dextrin-A from Amylopectin.—A sample of amylopectin, which had been isolated from potato starch by fractional precipitation with thymol (Haworth, Peat, and Sagrott, *loc. cit.*) and had B.V., 0·216, was used as the substrate for the production of dextrin-A by the agency of soya bean β-amylase.

A suspension in cold water of the amylopectin (dry weight, 50·8 g.), which initially had been moistened with a small volume of alcohol, was slowly stirred into boiling water, giving an approximately 3% paste (1500 c.c.), which was rendered less viscous by the addition of sodium chloride (0·5 g.). After being boiled for 20 minutes longer, the solution was cooled to 35·5°, stirring being continued throughout the process. Meanwhile the enzyme solution was prepared by shaking soya bean β-amylase (0·40 g.) with distilled water (350 c.c.) for approximately 1 hour and removing the undissolved residue by the centrifuge. The enzyme solution and the paste were thoroughly mixed, accurately diluted to 2 l., covered with a layer of toluene, and incubated at 35·5°.

The progress of the amylolysis was followed by removing, at intervals, aliquot portions (1 c.c.) of the digest, which were diluted with sufficient water to permit accurate analysis for maltose by the Shaffer–Hartmann method. The weights of maltose in the digest were nil, 28·37 g., and 29·45 g. after zero time, 27 hours, and 42 hours respectively. To ensure completion of the reaction a further volume of β-amylase solution (0·10 g. in 50 c.c. water; prepared as above) was introduced at this stage. After total incubation times of 68 and 88 hours, 29·65 g. and 29·80 g. of maltose were present. The mean (29·63 g.) of the last three estimations was assumed to be the limiting amount of maltose, and, since some amylopectin (0·44 g.) which had not been gelatinised was recovered from the walls of the reaction vessel by hardening with alcohol, this value represented a 55·7% conversion into sugar. The relative constancy in the amount of maltose produced in 42—88 hours indicated the absence of all but a trace of α-amylase in the enzyme.

After being boiled for 10 minutes to inactivate the enzyme and filtered to remove coagulated protein, the filtrate was mixed with an equal volume of alcohol, which was sufficient to precipitate practically all the dextrin-A, leaving most of the maltose in solution. The product was hardened by grinding it with alcohol, washed with ether, and dried in a vacuum over phosphoric oxide. Yield, 22·8 g.(45·3%); ash, 0·55%; reducing power ≡ 1·6% maltose.

The remaining maltose and inorganic impurities were removed by dissolving the dextrin in warm water (1300 c.c.) and dialysing in cellophane bags against frequent changes of distilled water for 2 days. The residue was precipitated with alcohol (2 volumes), hardened, washed, and dried as above. Yield, 18·9 g. (37·5%; based on amylopectin); B.V., 0·200; reducing power <0·05% maltose. No change in either B.V. or reducing power was induced by boiling the dextrin in aqueous solution (50 mg. in 30 c.c.) for 3 minutes.

Further Treatment of Dextrin-A with β-Amylase.—Three digests having the following compositions were incubated under toluene at 35·5°.

Digest (A): dextrin-A (40 mg.), β-amylase solution (10 c.c.; 0·1% prepared as above), water (40 c.c.).
Digest (B): β-amylase solution (10 c.c.; 0·1%), water (40 c.c.).
Digest (C): dextrin-A (40 mg.), water (50 c.c.).

At intervals a portion (5 c.c.) of each digest was removed and the reducing power was estimated directly by the Somogyi method. The amounts of "apparent" maltose in the digests were (A), 1·02 mg. (13 and 17 hours); (B), 0·40 mg.(13 and 17 hours); (C), 0·00 mg. (13 and 17 hours). Therefore 0·62 mg. of maltose was produced by β-amylolysis in digest (A), representing 1·18% conversion into sugar.

Typical Digests Involving the Treatment of Dextrin-A with Saliva and Subsequently with Soya Bean β-Amylase.—(a) *Prolonged action of α-amylase (region R of graph).* The reducing power of the stock solution of mucin-free saliva, estimated by the Shaffer–Hartmann method, corresponded to 2·82 mg. of maltose/10 c.c. A portion of this enzyme was incorporated in digest (29), which contained: dextrin-A (50 mg.), mucin-free saliva (10 c.c.), and water (20 c.c.).

The digest was incubated at 15° for 2 hours and then boiled for 3 minutes, a process which had been shown to effect the complete destruction of the enzyme. The boiled solution was accurately diluted to 50 c.c., giving a standard solution of which 1 c.c. corresponded to 1 mg. of dextrin-A. Two aliquot portions (5 c.c. each ≡ 5 mg. dextrin-A) were withdrawn at this stage; the reducing power of the first portion, determined by the Shaffer–Hartmann method, indicated 4·05 mg. of "apparent" maltose. Thus the entire standard solution contained the equivalent of 40·5 mg. of maltose, 2·8 mg. being due to the saliva itself. The maltose (37·7 mg.) produced by α-amylolysis represented a 71·4% conversion of the dextrin-A.

The second portion (5 c.c.) of the standard solution was introduced into a graduated flask (500 c.c.) containing water (200 c.c.) and slightly acidified with hydrochloric acid (3 drops; 5N). After the addition of iodine–potassium iodide solution (5 c.c.; 0·2% iodine in 2% potassium iodide) it was diluted to 500 c.c. and left for several hours. The A.V. (6800 A.) revealed that the polysaccharide no longer stained with iodine, the fall in A.V. (6800 A.) during α-amylolysis being 100%.

To the remainder of the standard solution (40 c.c. ≡ 40 mg. dextrin-A) was added β-amylase solution (10 c.c.; 0·1%, prepared as above). This digest was incubated at 35·5° under toluene, the reducing power in aliquot portions being estimated periodically by the Shaffer–Hartmann method. After 2, 21, and 27 hours, the "apparent" maltose was 32·4, 33·8, and 34·1 mg., the mean of the last two readings being accepted as the limiting concentration. Since 2·2 mg. and 0·4 mg. were contributed by the saliva and β-amylase themselves, 31·4 mg. had been produced by the consecutive actions of these two enzymes from dextrin-A (40 mg.), representing a 74·3% conversion.

(b) *Less drastic treatment with saliva. Addition of maltose* (*region L of graph*). Part of the stock solution of mucin-free saliva was diluted 200-fold. Its reducing power was thereby diminished to a value (0·014 mg./10 c.c.) which made a negligible contribution to the reducing power of the following digest (19): dextrin-A (50 mg.), maltose (15·9 mg.), diluted mucin-free saliva (200-fold; 10 c.c.), and water (20 c.c.). When the incubation had proceeded for 30 minutes at 15°, the α-amylase was destroyed by boiling and the experiment was continued as in (a).

The Shaffer–Hartmann method revealed that the standard boiled solution remaining after α-amylolysis contained 19·1 mg. of maltose. Of this, 15·9 mg. had been introduced deliberately and thus 3·2 mg. resulted from enzyme action, the conversion being 6·06%. The A.V. (6800 A.) was 52·2% of that given by the dextrin-A under similar conditions.

During the subsequent action of β-amylase the limiting amount of maltose (21·2 mg.) was reached after 16 hours. Since 12·7 mg. had been introduced deliberately (3·2 mg. had been removed for the 2 estimations) and 0·4 mg. was contributed by the β-amylase itself, 8·1 mg. of maltose had been produced from dextrin-A (40 mg.); a conversion of 19·2% had been effected by the two enzymes.

(c) *Less drastic treatment with saliva. No maltose added* (*region L of graph*). Again mucin-free saliva which had been diluted 200-fold was employed and its contribution to the reducing power of the digest could be neglected. The digest (30), which was incubated at 15° for 5 minutes, contained: dextrin-A (50 mg.), diluted mucin-free saliva (200-fold; 10 c.c.), and water (20 c.c.).

The solution was boiled for 3 minutes and accurately diluted to 50 c.c. A portion (5 c.c.) of this standard solution, when stained with iodine as in (a), showed a 23·5% reduction in A.V. (6800 A.). A second portion (5 c.c.), analysed directly by the Somogyi method, contained 0·109 mg. of maltose, making a total of 1·09 mg. in the entire standard solution. This represented a 2·06% conversion into maltose by α-amylase.

The remainder (40 c.c. ≡ 40 mg. dextrin-A) was incubated with β-amylase (10 c.c.; 0·1% solution, prepared as above) under toluene at 35·5°. Aliquot portions (5 c.c.), analysed by the Somogyi method, contained 0·66 mg. of maltose when the limit was reached. Thus 6·6 mg. were present in the digest, 0·4 mg. being contributed by the β-amylase itself and 6·2 mg. resulting from the two enzyme actions, representing a 14·7% conversion of the dextrin-A.

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178. *The Properties of Freshly-formed Surfaces. Part VII. The Application of the Vertical-plate Technique to the Study of Soluble Films at Air–Liquid and Liquid–Liquid Interfaces.*

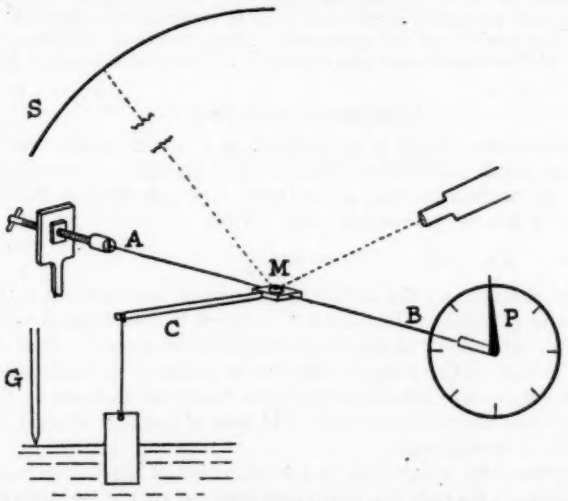
By C. C. ADDISON and S. K. HUTCHINSON.

The vertical-plate method, applied by previous workers to the study of insoluble monolayers, has been adapted for soluble-film measurements. In addition to single determinations of surface or interfacial tension, the method is suitable for time studies of short duration. The simple apparatus described is readily assembled, the essential features being a thin platinum plate and torsion wire. The procedure for ensuring zero contact angle is given. An accurate relation between the movement of the plate and the change in tension is calculated, and the theoretical calibration curves compared with those obtained experimentally. Advantages, and possible errors, arising from the wetting of the plate above the meniscus are discussed. Vertical-plate measurements involve the minimum of surface expansion during a determination, and the method has been developed with the object of comparing the results with those obtained at expanding surfaces (following papers).

THE vertical-plate technique devised by Wilhelmy (*Ann. Physik*, 1863, **119**, 177) was developed by Harkins and Anderson (*J. Amer. Chem. Soc.*, 1937, **59**, 2189) and found to be at least as

suitable for studying the compression of insoluble films as the horizontal-film balance, although Alexander and Teorell (*Trans. Faraday Soc.*, 1939, **35**, 1200) found the method limited in application. Dervichian (*J. Phys. Radium*, 1935, **6**, 221; *J. Chem. Physics*, 1939, **7**, 932) incorporated a device for the automatic recording of force–area curves. These workers maintained a constant vertical force on the plate by attaching it to one arm of an analytical balance. In Ruyssen's experiments (*Rec. Trav. chim.*, 1946, **65**, 581) on saponin solutions the vertical force was varied by means of a chainomatic balance, in order to maintain the plate in the same position with respect to the surface, thus eliminating the buoyancy factor. Andersson, Ställberg-Stenhagen, and Stenhagen (" The Svedberg ", Almqvist and Wiksells, Uppsala, 1944) replaced the analytical balance by a torsion wire, and employed automatic recording. To overcome variations in contact angle at liquid–liquid interfaces, Alexander and Teorell (*loc. cit.*) suggested that the plate be made uniformly hydrophobic by depositing a film of ferric stearate, and Cheesman (*Arkiv Kemi, Min. Geol.*, 1946, **22B**, i, 1) has successfully employed a uniform coating of carbon for this purpose.

FIG. 1.



These modifications of the vertical-plate technique have been developed primarily for the study of insoluble monolayers. The method has been little used in work on soluble films, probably because for pure liquids and many solutions it offers few, if any, advantages over the many other simple and accurate methods already available for surface-tension measurement. However, in the course of experiments on the expansion of soluble films (Parts VIII and IX, following papers) it became necessary to determine the surface tension of various solutions under conditions involving minimum expansion of the surface. Several of the standard methods for surface-tension measurement involve considerable expansion of the surface either during the determination (*e.g.*, drop-weight and bubble-pressure methods) or at the moment when the tension is recorded (*e.g.*, the ring method). The vertical plate does not suffer from this disadvantage, and the surface tensions can be derived without the use of empirical correction factors.

In adapting the technique to soluble-film measurements, the following considerations are important. (1) The relative positions of the plate and the surface must be easily adjustable, to ensure zero contact angle; (2) when the method is used for the study of rates of adsorption, decreasing tensions are involved (these conditions resemble the compression of insoluble monolayers, but high sensitivity is essential); (3) during expansion of a soluble film, the tension rises (therefore the instrument should be capable of recording tension during the falling of the plate). The torsion-wire technique described below satisfies these requirements, and the apparatus may be readily assembled from material normally available.

EXPERIMENTAL.

The arrangement of the apparatus is shown diagrammatically in Fig. 1. The torsion wire *AB* was of phosphor-bronze, 0·032 cm. in diameter, 23 cm. long, and was free from fatigue. The end *A* was held in a chuck attached to a screw, and was fixed in position by means of locking nuts. The lever arm *C* was of aluminium, 11 cm. long. The plate was supported by a platinum wire which passed loosely through

holes in arm C and the plate, thus ensuring that the plate remained vertical during a determination. Measurements were conducted with both glass and platinum plates, and were found to be more reproducible when platinum was used; this was attributed to the greater ease with which the platinum surface could be cleaned; between each measurement the plate (2·24 cm. wide, 5 cm. long, and 0·0033 cm. thick) was washed with distilled water, wiped with a fine cloth, washed again, and heated in a flame to a white heat.

Movement of Plate.—The variation in the position of the plate produced by change in surface tension was magnified by attaching a mirror M to the junction of the arm C and the torsion wire. A spotlight and hair-line were reflected on to a circular scale S, arranged with its centre at M and 84·5 cm. distant, giving a magnification of about 15.

Position of Surface.—In preliminary experiments the surface was maintained at a constant and predetermined level by viewing it through a microscope carrying an eye-piece scale. In view of the difficulty of setting a liquid–liquid interface accurately by this method, it was found more convenient (and sufficiently accurate) in later experiments to raise the level of the liquid to the tip of a glass rod G drawn to a point. Two such rods were used in work at liquid–liquid interfaces. For the study of time or surface-expansion effects the liquid may be contained in a trough. For single measurements on a series of solutions, a circular (inverted conical) vessel, giving a liquid surface 15 cm. in diameter, was used. This vessel carried a run-off tap, so that the liquid could be completely drained away and the vessel refilled with fresh solution to the tip of the glass rod. The vessel carried a transparent cover (slotted to accommodate the glass rods and plate suspension wire) to minimise evaporation.

Position of Plate.—The position of the plate with respect to the surface was controlled by the pointer P, to which the end B of the torsion wire was attached. P moved freely over a 360° dial, and carried a lens for accurate setting.

Discussion and Results.

A vertical platinum plate, width w and thickness t, when partly immersed to a depth l in water of density d and surface tension γ, will attain a position of equilibrium when the weight W_g of the plate, plus the surface tension acting on it, are balanced by the upthrust of the water, plus the vertical force F due to the torsion wire. Thus

$$2(t + w)\gamma + Wg = twdlg + F \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In any series of measurements the setting of pointer P is standard, so that both ends of the torsion wire are fixed in position. The force F exerted by the torsion wire depends upon, and varies with, the vertical movement of the plate and the lever arm C. It is convenient to arrange the initial setting of end A of the wire so that the wire has a clockwise torque in the direction $A \longrightarrow B$ (Fig. 1), in which case lifting of the plate involves decrease in the torsion. The fact that the torque in the two halves of the wire AM and MB is not altered to the same extent by change in position of C is immaterial.

If the water is replaced by a solution of a surface-active agent (sufficiently dilute that the density is not appreciably affected) the plate will rise out of the liquid a distance Δh until the decrease $\Delta\gamma$ in tension is balanced by the decrease in buoyancy, plus the decrease in F. Thus

$$2(t + w)\Delta\gamma = twdg\Delta\mathrm{h} + \Delta F \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Δh is magnified on the scale S. If ΔS represents the difference between the scale readings for pure water and for the solution, then $\Delta S = 2y\Delta h/x$, where x is the length of arm C and y is the distance MS. Therefore

$$\Delta\gamma = K_1\Delta S + K_2\Delta F \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $$K_1 = twdxg/4y(t + w) \text{ and } K_2 = 1/2(t + w)$$

K_1 and K_2 are therefore constants of the apparatus, and had values 0·105 and 0·223 respectively for the apparatus and settings employed.

In order to relate $\Delta\gamma$ and ΔS, it is necessary to obtain ΔF in terms of ΔS. The assumption that ΔF and Δh (and thus ΔS) are proportional is only justified for very small values of Δh. To avoid this assumption, the pointer P was fixed at the standard position, known weights suspended from the end of arm C, and the S–F relation graphed directly. From this accurate curve, the F values corresponding to the S readings for water and solution can be obtained. The difference between these F values is the ΔF term of equation (3). It will be clear from the above calculations that water is not a necessary standard. Any solution may serve as standard, provided that its surface tension under the static conditions of the experiment be known.

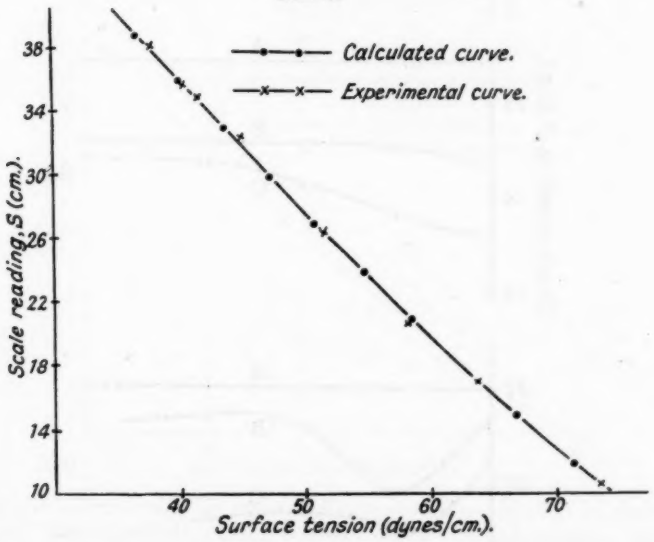
Sensitivity.—The sensitivity of the apparatus (*i.e.*, $\Delta S/\Delta\gamma$) may be controlled by three methods: (*a*) by adjustment of the length of arm C and the mirror-scale distance, (*b*) by varying the dimensions of the plate, and (*c*) by using different torsion wires, thus varying the significance of the ΔF term in equation (3).

Method (*a*) is undesirable since it involves structural alterations to the apparatus; method (*b*) provides the widest range of sensitivity. In studying changes of surface tension with time,

tension ranges up to 30 dynes/cm. may be encountered, and it is essential to adjust the sensitivity of the apparatus to the anticipated tension range. Maximum sensitivity was therefore obtained by employing the thinnest platinum plate consistent with rigidity (0·0033 cm. thickness was found suitable), and this high sensitivity was then diminished where necessary by changing the torsion wire. It is a major advantage of the present technique that the same plate may be used throughout an investigation, irrespective of sensitivity.

Applicability of Equation (3).—The γ–S relation has been calculated by using equation (3), and compared with that obtained by direct measurement of γ and S for a series of *iso*amyl alcohol solutions at 15°. In deriving the theoretical curve, water was taken as standard, γ being taken as 73·6 dynes/cm. at 15°. *iso*Amyl alcohol was selected as solute because the surface tension of its solutions reaches the static value within 0·1 sec. (Addison, *J.*, 1944, 252). Again, drop-weight measurements at various flow rates have shown that the solutions are not influenced by surface expansion, and therefore the surface-tension values obtained by the drop-weight method are also those operating at the static surfaces used in the vertical-plate experiments. Fig. 2 indicates that agreement is good, and that equation (3) correctly interprets the behaviour of the vertical plate at the air–water interface.

FIG. 2.

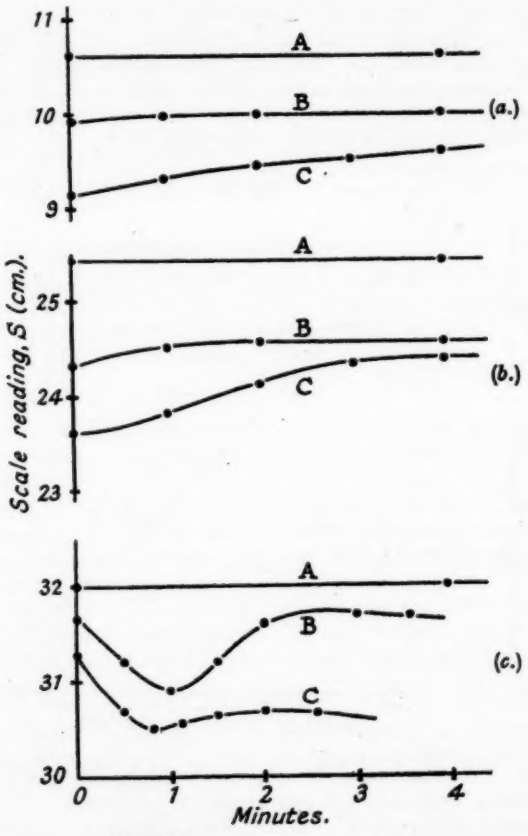


Wetting of the Plate.—To obtain reproducible values for $\Delta\gamma$, the plate was partly immersed in the liquid, and then raised until zero contact angle was obtained; the zero angle was readily observed by direct viewing of the plate. Again, when pointer P was moved at a uniform rate, the movement of the spotlight over scale S was erratic until the contact angle became zero; thereafter, its movement was smooth. If the plate is raised beyond the distance necessary for the formation of zero contact angle, it supports a film of liquid above the meniscus. With thin plates, the weight of this film introduces an error into the readings, the drainage of the film gives rise to a drift in the S value with time, and close control over the distance through which the plate is raised after initial immersion is therefore essential. In each determination, pointer P was set at an angle below the standard position at which the apparatus was calibrated, and the plate gently lowered into the liquid. The pointer was then raised to the standard position, and the length of wetted plate was thus determined by the extent of this final adjustment of P. Figs. 3(*a*), (*b*), and (*c*) show the drifts obtained with water and *iso*amyl alcohol solutions: the approximate length of wetted plate, and the angle representing final adjustment of P, are given for each curve. With distilled water, a length of wetted plate exceeding about 0·5 cm. gave rise to drainage drifts, and the weight of liquid in 0·5 cm. of film introduces an error of about 0·6 dyne/cm. into the tension reading. Similar results were obtained with 0·5% *iso*amyl alcohol solutions, but at higher concentrations of alcohol (Fig. 3, *c*) any exposure of wetted plate gave rise to erratic readings. Ridges of solution were observed to rise and fall on the wetted portion of the plate above the meniscus, and may be of the type studied by Satterly and Stuckey (*Trans.*

Roy. Soc. Canada, **1932, 26, 131**). In no case was a drift obtained when the plate was raised just sufficiently to ensure zero contact angle.

Measurement of Increasing Tensions.—A technique similar to the above may be employed in the study of increases of surface tension over short time intervals. The plate is wetted to a distance slightly in excess of that which it is anticipated the plate will fall during the experiment. Provided that the time intervals are so short that the liquid film on the plate does not evaporate, a zero contact angle is maintained during the falling of the plate. If the error in the tension readings (less than 1 dyne/cm.) due to the presence of the liquid film on the plate is significant in

FIG. 3.



(a) *Water.*
(b) 0·5% iso*Amyl alcohol solution.*
(c) 1% iso*Amyl alcohol solution.*

Curve.	Length of wetted plate, cm.	Pointer adjustment.
A	0—0·1	5°
B	0·5	10
C	1·0	15

comparison with the tension range involved, it may be calculated from the known length of wetted plate, and the values corrected.

Liquid–Liquid Interfaces.—The procedure outlined above has been successfully applied to liquid–liquid interfaces. The plate was suspended partly in the lower aqueous phase, and partly in the upper oil layer, and only the suspending wire penetrated the oil surface. As the interfacial tension decreases, the plate again rises until $\Delta\gamma$ is balanced by (*a*) the decrease in buoyancy forces on the plate at the interface, and on the wire at the oil surface, and (*b*) the decrease in F. Thus for zero contact angle

$$2(t + w)\Delta\gamma = tw\Delta h(d - d_2)g + \pi r^2 d_2 g\Delta h + \Delta F$$

where d_2 = density of the oil and r = radius of the suspension wire. This reduces to

$$\Delta\gamma = K_3\Delta S + K_4\Delta F \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

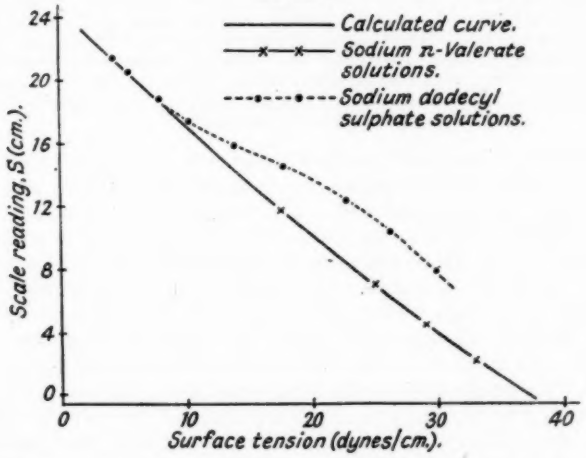
K_3 has the same value as in equation (3), and K_4, which is again a constant of the apparatus, has the value

$$[tw(d - d_2)gx + \pi r^2 x d_2 g]/4y(t \times w)$$

thus including both buoyancy factors.

To obtain zero contact angle, close control over the position of the plate with respect to the interface is again essential, and it was found necessary at interfaces to raise the plate through approximately twice the distance required at the air–liquid interface, before the contact angle fell to zero. With all aqueous solutions tested, the meniscus crept down the plate when the latter was raised beyond the distance required for formation of a zero contact angle, so that at interfaces no "wetted-plate" difficulties arise. With solutions of strongly surface-active substances, no detectable alteration in contact angle occurred during 15 minutes, so the apparatus may be applied to time studies of short duration. With water and solutions of high interfacial tension, the contact angle increased irregularly over several minutes, but remained at zero for a sufficient time (30—60 seconds) after the initial lifting of the plate to enable an accurate

FIG. 4.



reading of the interfacial tension to be taken. To conduct time studies of short duration with the latter solutions, the sensitivity of the apparatus may be increased so that the distance through which the plate rises as tension decreases is sufficient to maintain a zero contact angle. However, it has not been found possible to maintain zero contact angle at the interface as the plate falls, so that with the present apparatus time studies involving increase in tension are restricted to the air–liquid interface.

By employing equation (4), the theoretical γ–S curve has been calculated (Fig. 4), the water–toluene interface being used as standard, and γ being taken as 36·6 dynes/cm. at 15°. Under these conditions $K_3 = 0{\cdot}0375$. To confirm the applicability of this calibration curve, S values were measured for a series of sodium dodecyl sulphate solutions. The drop-volume method was used in determining the interfacial tensions because of its accuracy. The broken curve (Fig. 4) shows that agreement is ideal at tensions below 8 dynes/cm., but that at higher values a considerable discrepancy arises. A subsequent investigation (Part IX) has shown that for these more dilute sodium dodecyl sulphate solutions the interfacial tension at an expanding surface (*i.e.*, as recorded by the drop-volume method) is appreciably higher than that at a stationary surface. This expanding-surface effect is only operative at concentrations below 0·005M, and it is of interest that this is also the concentration below which the discrepancies (Fig. 4) occur.

To confirm the theoretical curve over the higher tension ranges it was therefore necessary to employ a short-chain solute. As with air–liquid interfaces, the liquid–liquid interfacial tension of such solutions is not influenced by surface expansion, and the tension values measured with accuracy by the drop-volume method are again those operating on the vertical plate. However, most short-chain alcohols and carboxylic acids have appreciable solubility in toluene, and the

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hydrolysis of salts of aliphatic carboxylic acids also gives rise to migration of acid across the interface. These difficulties were overcome by dissolving *n*-valeric acid in 2N-sodium hydroxide solution, and diluting the solution with 0·1N-sodium hydroxide solution to suppress hydrolysis. The densities of the solutions were then restored to that of water by further slight dilution or addition of alkali. By this means stable S readings were obtained over the tension range 17—36·6 dynes/cm. (employing up to 6% *n*-valeric acid) and the γ–S points in this range are recorded in Fig. 4. Agreement with the theoretical curve is ideal, and equation (4) therefore interprets correctly the behaviour of the vertical plate at liquid–liquid interfaces.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, June 21st*, 1947.]

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179. *The Properties of Freshly-formed Surfaces. Part VIII. Expansion of Soluble Films of Decoic Acid at the Air–Water Interface.*

By C. C. ADDISON, J. BAGOT, and H. S. MCCAULEY.

The theoretical tensions operating at the surface of drops expanding at known rates have been calculated from (*a*) the surface tensions of decoic acid solutions at stationary (*i.e.*, non-expanding) surfaces recorded in Part VI (*J.*, 1946, 579) and (*b*) measurements of the volume–surface area relation for expanding drops. These calculations assume that the surface activity of an adsorbed molecule is not influenced by expansion of the surface, and the calculated values of tension are appreciably lower than those actually observed. Possible reasons for the decrease in surface activity of a soluble film during expansion of the surface are discussed. Change in orientation of the adsorbed molecules provides the most satisfactory explanation of the effect, which is common to other long-chain adsorbates.

NUMEROUS investigations have confirmed that the surface tension of a solution depends upon the state of the surface as well as the bulk concentration of the solute, and may therefore vary with the method of measurement employed. The amount of adsorbed material in an insoluble film is known and constant, and this enables a ready interpretation of surface pressure–surface area curves to be made on the basis of state and orientation of the adsorbed layers. However, similar studies of soluble films are complicated by two factors. First, the interchange of solute between surface and bulk solution which occurs as surface area changes nullifies the variations in surface pressure which would otherwise result; for instance, Ford and Wilson (*J. Physical Chem.*, 1938, **42**, 1051), studying the compression of soluble films of phenol, β-phenylpropionic acid, and octoic acid, by a piston film of oleic acid, found that, although aged surfaces presented some resistance to the spread of oleic acid, fresh surfaces showed no such resistance. Secondly, few direct determinations of the surface excess of adsorbate have been made, and quantitative treatment of soluble films must usually rely upon the application of the Gibbs equation. The expansion or contraction of a fresh soluble film has not hitherto been considered to have any significant influence on the surface activity of the adsorbed molecules, although surface expansion is a feature common to several of the standard methods of surface tension measurement. However, the following results for decoic acid indicate that surface activity may be decreased to an appreciable extent during surface expansion, and these studies have been extended to other solutions (see Part IX, following paper) in view of the information they may provide on orientation of long-chain molecules at interfaces.

The surface tension of a solution may be influenced by surface expansion in at least two ways: the tension may rise owing to dilution of the surface layer, and it may vary with change in orientation in the film. (The term orientation is used here for simplicity, and its use does not exclude the possibility that change in position of adsorbed molecules with respect to the plane of the surface, as well as change in angle, may occur.) In most solutions of appreciable concentration, the first factor may be neglected; thus the changes in surface tension observed on expanding the surface of solutions of sodium dodecyl sulphate (Part IX) may be suitably explained by the orientation effect alone. However, such measurements provide no evidence that a given number of molecules adsorbed on unit area of a stationary (*i.e.*, non-expanding) surface produce a lowering of the tension which is different from that at an expanding surface. In this paper an attempt is made to obtain quantitative proof of this effect; this has been achieved by studying the decoic acid system, in which dilution of the surface, and change of orientation during expansion, can both influence the measured tensions. It has already been shown (Part VI, *J.*, 1946, 579) that the surface tensions as measured by the drop weight method may vary over a range of 20 dynes/cm. with rate of expansion of the drop surface.

Scheme of Calculation, and Use of the Gibbs Equation.—Adam ("Physics and Chemistry of

Surfaces", Oxford Univ. Press, 2nd edtn., 1938, p. 118) has found striking agreement between experimental results and those calculated by using the Gibbs equation for the C_{12} carboxylic acid, and Ford and Wilson (*loc. cit.*) have obtained fairly close agreement for the C_8 acid. Therefore the equation is probably applicable with sufficient accuracy to the equilibrium tension–concentration curves for the dilute decoic acid solutions used; it is to be emphasised, however, that no conclusions given below depend upon the exact quantitative applicability of the equation, and that the equation is not applied directly to expanding surfaces. The equilibrium tensions at various concentrations reported in Part VI (*loc. cit.*) have been substituted into the approximate form of the Gibbs equation to derive a Γ–γ relation for decoic acid solutions. From a knowledge of the change of surface tension with time at a *stationary surface*, the Γ–γ relation is used to determine the rate of development of the stationary surface film. (These calculated quantities of adsorbed acid may without disadvantage be a fraction or a multiple of the real amounts.) For a given rate of surface expansion, the amount of adsorbate present on the expanding surface is deduced. The Γ–γ relation is then used to obtain the theoretical tensions at surfaces expanding at known rates, it being therefore assumed in these calculations that no change in the surface activity of an adsorbed molecule occurs during expansion. The calculated

FIG. 1.

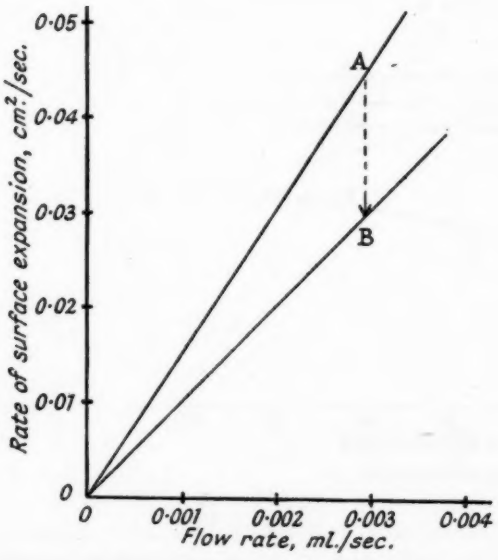
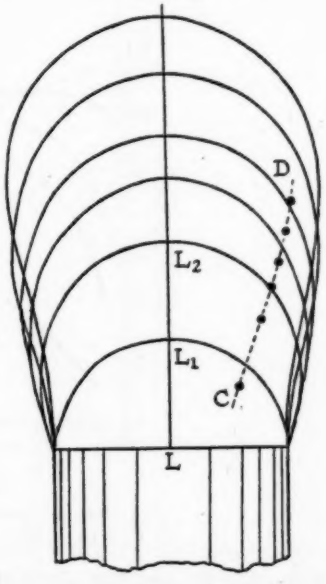


FIG. 2.



tensions are then compared with the experimental values, in which any change in surface activity due to surface expansion will be reflected. The general conclusions concerning the effect of surface expansion on surface activity, reached by this theoretical treatment, agree closely with the effects observed by direct measurement on a solute of similar chain length (Part IX).

EXPERIMENTAL.

Surface Tension–Time Relation for a Stationary Surface.—The technique employed and the results obtained for decoic acid solutions up to the solubility limit of 0·005% ($2{\cdot}91 \times 10^{-4}$M) have been reported in Part VI (*loc. cit.*). Drops of solution of predetermined volume were formed rapidly on a calibrated orifice. When the tension fell to a value equivalent to the drop weight, the drop fell away, thus recording both surface tension and surface age. By repetition with different initial drop sizes, tension–time curves were obtained (Part VI, Fig. 2) which showed a fall in tension from the value for pure water to the equilibrium tension in time intervals from 10 seconds ($2{\cdot}85 \times 10^{-4}$M) to 6 minutes ($0{\cdot}466 \times 10^{-4}$M).

Expanding Surfaces.—It is necessary in these experiments to measure the surface tension without disturbing the surface. The gradual development of a drop of the solution in air satisfies these requirements, and has the advantage that the surface area involved is small, promoting uniformity. The application of this technique to decoic acid solutions has also been described in Part VI (*loc. cit.*). The variation in surface tension of a $1{\cdot}16 \times 10^{-4}$M-solution with rate of flow of liquid into the drop is shown in Fig. 9 (experimental curve) and the shape of the curve is similar for all concentrations (Part VI, Fig. 8). The expanding-drop technique has the disadvantage that for a constant liquid-flow rate, the rate of expansion of surface is not uniform throughout the life of a drop. For the orifice used (0·27 cm. outside diameter) the relation between flow rate and rate of surface expansion is shown in Fig. 1. The

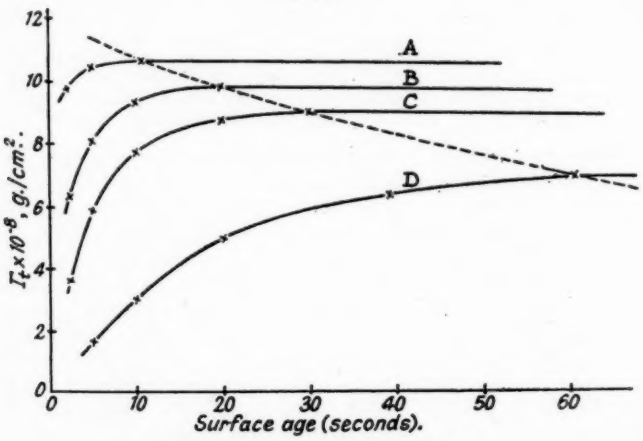
upper line *OA* represents the maximum rate of expansion (calculated from the surface-area measurements in Fig. 4) for any given flow rate, and is operative when the drop first forms. As the drop increases under constant flow rate, the rate of surface expansion decreases over range *AB* to line *OB*. Nevertheless, the variation in rate of expansion during a drop life does not exceed one-third of the range available by altering the flow rate. It has been found convenient to relate surface tension with rate of flow of liquid, and in calculating the theoretical tensions at the surface of an expanding drop, account is taken of this variation in rate of surface expansion.

Relation between Surface Area and Volume of Expanding Drop.—The image of the drop was projected by means of a long-focal-length achromatic lens on to a distant screen, giving a linear magnification of 21. The orifice was attached to a calibrated capillary tube carrying a mercury thread, and it was thus possible to expel known volumes of liquid. The image was received on a photographic paper screen; the drop volume was increased in stages, and a series of superimposed shapes recorded photographically (Fig. 2). Wires were then fitted to each of the semi-perimeters, and the centroid of each shape obtained by suspending the wire from several points on silk thread. As the drop expands the centroids follow the smooth curve *CD*, and the positions of these centroids for six different volumes are shown in Fig. 2. The distance of the centroid from the axis of the drop can be measured, and the surface area calculated by Guldinus's theorem.

Discussion and Results.

Γ-t *Relation.*—The static and dynamic surface tensions of decoic acid solutions at a stationary surface are recorded in Part VI, Fig. 2. The static values have been plotted against the

Fig. 3.



Decoic acid concentration (M).

A, $2{\cdot}85 \times 10^{-4}$. B, $1{\cdot}74 \times 10^{-4}$.
C, $1{\cdot}16 \times 10^{-4}$. D, $0{\cdot}64 \times 10^{-4}$.

concentration C, and the slope of this curve at various C values substituted into Gibbs's adsorption equation $\Gamma_2^{(1)} = (\mathrm{d}\gamma/\mathrm{d} \log fC)/\boldsymbol{RT}$ to determine the relation between surface excess Γ of component (2), *i.e.*, decoic acid, and surface tension. The dynamic surface tensions can then be transposed into Γ values, and the curves obtained (Fig. 3) show the development of surface excess with time at 20°. The activity coefficient f has been taken as unity in these calculations. The broken line represents the boundary between dynamic and equilibrium surfaces. Since static tensions were used in deriving Γ_t (Fig. 3), each value of Γ_t represents a surface excess in the state of orientation which holds at a stationary surface.

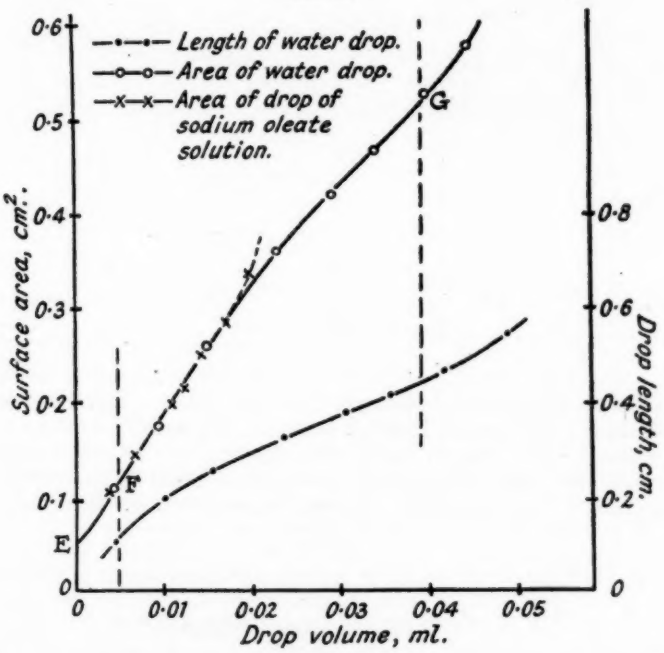
Surface Area of an Expanding Drop.—The area–volume relation for pure water at 20° is shown in Fig. 4. The curve falls into 3 distinct stages: (1) Represented by *EF*; in this range the volume is increasing to that of a hemisphere standing on the orifice, and $\mathrm{d}A/\mathrm{d}V$ is increasing. (2) Represented by *FG*; this stage approaches closely the form of curve $A = aV^b$ given by an expanding sphere; the constant $a = 5{\cdot}37$ and $b = 0{\cdot}73$ (compared with $a = 4{\cdot}84$ and $b = 0{\cdot}667$ for an expanding sphere). (3) Immediately before falling away, the drop elongates rapidly, and $\mathrm{d}A/\mathrm{d}V$ again becomes an increasing quantity.

The lower curve (Fig. 4) shows the variation in drop length (*i.e.*, distances LL_1, LL_2, etc., in Fig. 2) with volume, and it is clear that the more rapid increase in area in stage (3) coincides with elongation of the drop. Photographs showed that, with an orifice of 0·27 cm. outside diameter, the liquid remaining outside the plane of the orifice after the falling away of the drop was almost exactly the amount required to form a hemisphere on the orifice, and stage (1) of the curve was

therefore not significant in these experiments. For orifice diameters exceeding about 0·4 cm. the remaining liquid is insufficient to form a hemisphere, and stage (1) becomes significant.

During the development of a drop of decoic acid solution, the surface tension changes as well as the drop volume. Since the shape of a pendant drop of given volume varies with the surface tension, it was essential to test the effect of tension changes on the curve in Fig. 4 before the curve could be applied quantitatively. A second curve was therefore obtained by using a sodium oleate solution, $\gamma = 34$ dynes/cm. The experimental points are recorded in Fig. 4. As a result of the low γ value the drop falls away at a lower volume, but the operative second stages of each curve show close agreement. It was also confirmed that within the range of flow rates used, the shape of the drop at any stage was independent of its rate of development.

FIG. 4.



Calculation of Surface Concentration at an Expanding Surface.—During the expanding-drop experiments the solution left the orifice in a series of drops, the drop volume being constant for a given flow rate. The liquid remaining outside the orifice after the release of a drop reverted instantaneously to hemispherical form, so that for each drop the surface area at zero time was that of a hemisphere on the orifice. For a particular flow rate, the area–volume curve (Fig. 4) is readily converted into an area–time curve (not reproduced). Therefore the following information is now available for a given concentration and flow rate: (1) the rate of development of surface excess (Fig. 3) at a stationary surface; (2) the rate of expansion of the surface, and the rate of development of surface excess at an expanding surface may be deduced as follows:

The expansion of the surface can be regarded for calculation as proceeding in a series of small increments. Thus in the first small interval of time $0 \longrightarrow \delta t$, a surface excess $\delta\Gamma$ will have accumulated at the stationary surface. The surface can then be regarded as expanding instantaneously from A_0 (the area of the hemisphere) to $A_0 + \delta A_0$, and the surface concentration will be reduced to $A_0\delta\Gamma/(A_0 + \delta A_0)$, represented in Fig. 5 by point L. Therefore after period δt the surface condition is equivalent to point S on the stationary curve, and during the second interval $\delta t \longrightarrow 2\delta t$ adsorption will proceed along LM, where LM is parallel to the stationary-surface curve beyond S. The surface now expands $A_1 \longrightarrow A_1 + \delta A_1$ (where $A_1 = A_0 + \delta A_0$) and the surface excess represented by M is thus reduced by the fraction $A_1/(A_1 + \delta A_1)$ to point N. (The fraction by which the surface excess is reduced at the end of each δt period will not be a constant, since the area–time relation is not linear.) The development of Γ at an expanding surface is therefore represented by the broken line through L and N.

The above deductions are based on the assumption that at zero drop life the surface contains no excess of solute. This, however, is by no means certain. The hemisphere of liquid from which the drop starts is formed by contraction of the neck of liquid which joins the orifice and drop immediately before drop release; the initial surface may therefore contain any amount up to that corresponding to the static surface tension. The surface being assumed to have this

FIG. 5.

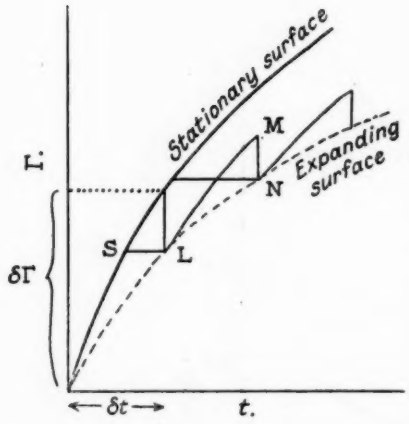
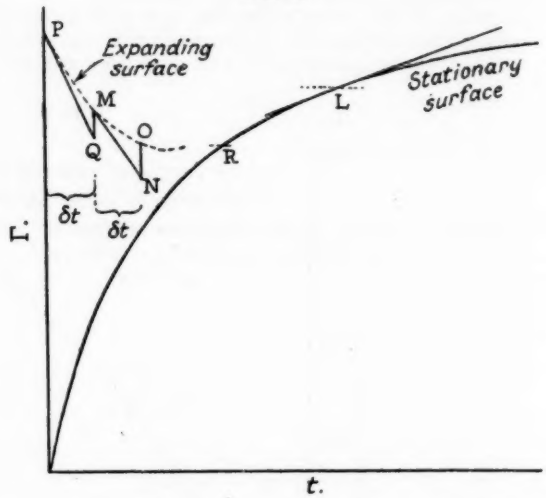
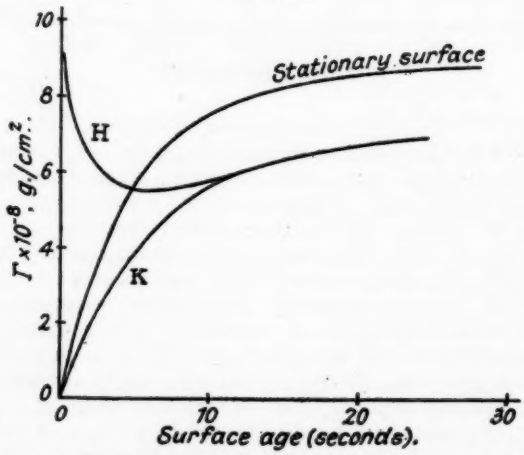


FIG. 6.



maximum amount of surface excess at zero time, the variation of Γ with time may be deduced as follows. The full line in Fig. 6 again represents the development of Γ at a stationary surface, and Γ increases to a maximum value (Γ max.) shown at P, which now represents the state of the expanding surface at zero time. During the first time interval δt, the surface excess will be reduced to $A_0\Gamma_{max.}/(A_0 + \delta A_0)$ (point Q). Further adsorption will therefore occur, at a rate

FIG. 7.



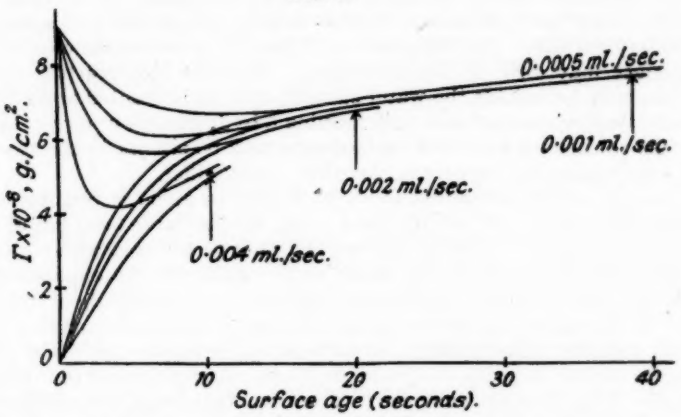
H, *expanding surface with maximum surface excess at zero time.*
K, *expanding surface with no surface excess at zero time.*

given by the tangent to the stationary-surface curve at L, where L represents the average surface concentration during the interval δt. This adsorption will increase the surface excess by an amount $(d\Gamma/dt)_L.\delta t$ represented by QM. During the second δt interval the surface expansion reduces the surface excess (represented by M) by the fraction $A_1/(A_1 + \delta A_1)$ to N; adsorption will have proceeded to an amount represented by NO and equal to $(d\Gamma/dt)_R.\delta t$, where the Γ value

of R is the mean of the values for M and N. Therefore if the surface carries its maximum excess of solute at zero time, the variation of Γ will be represented by the broken line PMO.

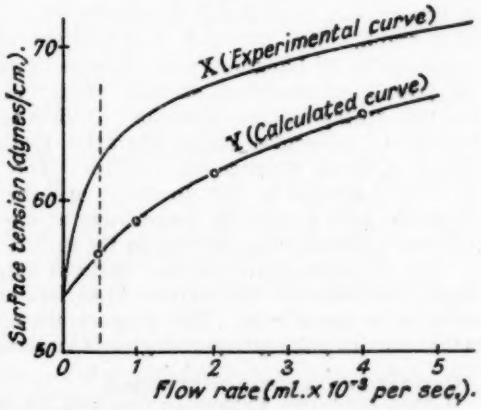
On the above basis, Γ–t curves have been calculated for a $1{\cdot}16 \times 10^{-4}$M (0·002%) decoic acid solution, and a flow rate of 0·002 ml./sec. (Fig. 7). Curve K assumes no surface excess, and curve H maximum excess, at zero time, and it is of immediate interest that the two curves coincide at higher t values. It follows that the common part of the curve represents the surface excess whatever the initial condition of the surface may be, and that provided measurements be made

FIG. 8.



over this time range, the initial condition of the surface is of no consequence. In order to verify that this feature was common to all rates of expansion, H and K curves for a concentration of $1{\cdot}16 \times 10^{-4}$M have been deduced for the four flow rates 0·0005, 0·001, 0·002, and 0·004 ml./sec., and are collected in Fig. 8. The results indicate that for a given concentration, the surface age at which the curves coincide is little influenced by rate of expansion. However, since the Γ values of the common curves represent a balance between rates of adsorption and surface expansion, slightly higher Γ values are reached at the lower flow rates. The vertical arrows (Fig. 8) are placed on the time axis at the surface age at which the drops would fall away from the 0·27 cm. orifice at each particular flow rate. At flow rates exceeding 0·004 ml./sec., the H and K curves do not coincide before the drop falls away; therefore comparisons between calculated and measured surface tensions have not been made for flow rates in excess of 0·004 ml./sec., since the measured values would not then be independent of the initial condition of the drop surface.

FIG. 9.



Comparison between Calculated and Experimental Surface Tensions.—Fig. 9 (curve X) shows the actual variation in surface tension which occurs in a $1{\cdot}16 \times 10^{-4}$M-decoic acid solution when rate of flow of liquid into the drop is varied. It is now possible to deduce this curve theoretically. The following example illustrates the method.

At a flow rate of 0·002 ml./sec., the drop weight was 0·0400 g., corresponding to a surface tension of 67·5 dyne/cm., as shown in curve X, Fig. 9. The drop life was 20·0 seconds, and reference to Fig. 8 indicates that after this time the surface contains $\Gamma = 6{\cdot}80 \times 10^{-8}$ g./cm.^{2}. The Γ–γ relation discussed above may then be employed to determine the surface tension corresponding to this excess, when $\gamma = 61{\cdot}7$ dynes/cm. (curve Y, Fig. 9). The remaining points on curve Y are determined similarly.

It is clear that a considerable discrepancy exists, and this is the case with other flow rates and concentrations also. The Γ–γ relation used in determining curve Y was derived using surface

tensions measured at a stationary surface, and curve Y thus represents the surface-tension values which would have obtained had the adsorbate present exerted the same surface activity as at a stationary surface. The fact that the experimental tensions are higher indicates that expansion of the surface renders the adsorbed molecules less efficient; *e.g.*, in the above example, the amount of adsorbate present on the expanding surface after 20 seconds lowers the surface tension from the water value (72·8 dynes/cm.) to 67·5 dynes/cm., whereas the same amount of adsorbate would lower the tension to 61·7 dynes/cm. if present at a stationary surface. The following factors may be responsible for this decrease in surface activity: (1) Association of decoic acid molecules may occur as a result of lateral adhesion at the surface. However, such association, which would probably reduce surface activity, is less likely to occur at an expanding than at a stationary surface. (2) The position of the decoic acid molecules with respect to the plane of the surface may differ in the two cases. Thus the hydrocarbon chains, which at a stationary surface may be outside the water surface, may be prevented at an expanding surface from fully penetrating the surface and thus forming a hydrocarbon exterior. (3) The degree of penetration of the surface by the decoic acid chains may be similar in the two cases, but their mean angle of orientation with respect to the surface may differ.

This effect cannot yet be attributed solely to change in angle of orientation, but available evidence supports this view. All soluble films so far studied have been found to be gaseous in state (Adam, *op. cit.*, p. 116). This will almost certainly be the case with expanding films, and it is feasible that orientation should be much more random at an expanding surface. It is significant that very slight surface expansion is necessary to bring about the full decrease in surface activity; at flow rates beyond the broken line in Fig. 9 the two curves are almost parallel. This is in accord with the disorientation hypothesis, since as soon as disorientation has been brought about, the surface activity should be no longer sensitive to further increases in rate of expansion. Again, it has been shown in Part VI (*loc. cit.*) that, while the stationary surface has a high temperature coefficient of tension, the tension at an expanding surface is not sensitive to temperature. The higher order of molecular orientation at a stationary surface is more likely to be subject to kinetic agitation, whereas the molecules adsorbed on an expanding surface, if already disorientated, are unlikely to be influenced appreciably by small changes in temperature.

It is not known to what extent the angle of orientation of adsorbed molecules in a soluble film influences their power to lower the tension (or even whether horizontal or vertical orientation represents the position of highest surface activity), so it is not yet possible to decide whether surface expansion brings the mean direction of the adsorbed molecules nearer the vertical or the horizontal position. From determinations of the work of adsorption in homologous series, Langmuir (*J. Amer. Chem. Soc.*, 1917, **39**, 1883 *et seq.*) deduced that adsorbed straight molecules in a stationary, soluble film lie parallel with the surface, and calculated (3rd Colloid Symposium Monograph, 1925, 75) that this position represents the lowest energy state. The general applicability of Langmuir's conclusions being assumed, then horizontal orientation represents the position of maximum surface activity, and the adsorbed molecules are deflected from this position during surface expansion. Evidence has been produced in Part IV (*J.*, 1945, 98) that long-chain molecules during migration to the surface are orientated with their hydrocarbon chains directed towards the surface. The adsorbate molecules may therefore penetrate a stationary surface in this direction, and then fall to the horizontal position of least energy. However, such a molecule penetrating an expanding surface may be prevented, by the impact of water molecules also arriving at the surface, from assuming the horizontal position.

The experiments on sodium dodecyl sulphate solutions described in Part IX (following paper) indicate that the decrease in surface activity on expansion of the surface is of the same order as for decoic acid. This supports the belief that the decrease is a function of chain length rather than of polar group or degree of ionisation.

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180. *The Properties of Freshly-formed Surfaces. Part IX. Expansion of Soluble Films of Sodium Dodecyl Sulphate at Air–Water and Toluene–Water Interfaces.*

By C. C. Addison and S. K. Hutchinson.

The deduction in Part VIII (preceding paper), that the surface activity of adsorbed long-chain molecules is decreased on expansion of the surface, is supported experimentally by measurements of the surface tension of aqueous solutions of sodium dodecyl sulphate at both stationary surfaces (by the vertical-plate method) and expanding surfaces (by the drop-weight method). Differences (up to 10 dynes/cm.) occur at all concentrations below 0·02M, and are attributed to disorientation of the adsorbed molecules during surface expansion. Interfacial-tension measurements against toluene show similar differences for solutions below 0·005M, but at higher concentrations surface expansion has no influence on the behaviour of the surface film. This is consistent with the anchoring effect of the toluene phase on the carbon chains, and a suitable explanation is again possible on the basis of disorientation.

It has been deduced in Part VIII (preceding paper) that expansion of a soluble film of decoic acid results in a decrease in the surface activity of the adsorbed molecules. The work now described was carried out in order to determine whether this decrease was common to other long-chain compounds, and to obtain direct experimental evidence of the surface-expansion effect. Some evidence of its existence is already available; for instance, the surface tensions of solutions of short-chain compounds (up to about C_8) determined by the vertical-plate and the drop-weight method show exact agreement (and the drop weight of such solutions is independent of the rate of formation of the drop), whereas the surface-tension values for a range of soap solutions (Cavier, *Compt. rend.*, 1941, **212**, 1146) and for solutions of bile (Boutaric, Berthier, and Roy, *Bull. Soc. Chim. biol.*, 1940, **22**, 170) measured by the ring-detachment method are as much as 8 dynes/cm. lower than the values obtained by the drop-weight method. Comparisons made during this work between the tension values given by the vertical-plate and the ring-detachment method for some long-chain compounds have indicated fairly close agreement. Therefore in some cases the expansion of a surface during detachment of a ring makes only slight difference to the recorded tension, presumably because the ring is already becoming detached before appreciable surface expansion occurs, and the discrepancies noted by Cavier (*loc. cit.*) may be due to surface expansion.

The changes in surface tension of decoic acid solutions on expansion of the surface have been attributed to two factors, *viz.*, the slow development of diffusion equilibrium and the change in orientation at an expanding surface. In order to make a separate experimental study of the second factor it is clearly essential to employ solutions in which any fall in surface concentration resulting from surface expansion is immediately replenished by diffusion from bulk solution. Sodium dodecyl sulphate was selected for these experiments because (*a*) having 12 carbon atoms, its migrational velocity will be high, and its high solubility permits its use in such concentration that the time required for the establishment of diffusion equilibrium is negligible, (*b*) hydrolysis does not occur, (*c*) the alkyl sulphates are completely dissociated in solution (Howell and Robinson, *Proc. Roy. Soc.*, 1936, *A*, **155**, 386), and (*d*) there is little doubt that the single long-chain ions represent the surface-active species (Powney and Addison, *Trans. Faraday Soc.*, 1937, **33**, 1243). Therefore any discrepancy between tension measurements at stationary and expanding surfaces must arise directly from expansion of the film. Considerable discrepancies have been found to occur at both air–water and toluene–water interfaces, and can be satisfactorily explained on the basis of molecular disorientation.

Experimental.

The surface and interfacial tensions at stationary surfaces were measured by the vertical-plate method described in Part VII (this vol., p. 930). Results were not reproducible if the platinum plate was wiped with filter-paper between each determination, because of the extreme sensitivity of these solutions to traces of metal ions. No such difficulties were encountered when a fine cloth, previously boiled in distilled water, was used. Surface tensions at expanding surfaces were measured by allowing drops of the solution to form gradually in air, and the rate of flow of liquid into the drop was controlled as described in Part VI (*J.*, 1946, 579). A similar technique was employed for interfacial tensions; the orifice was immersed in toluene, and the drop volume determined by counting the number of drops required to empty a calibrated bulb in the pipette. The same orifice was used as for the decoic acid experiments (Part VIII) and had an outside diameter of 0·27 cm. The major changes in tension were found to occur when the surface was expanding very slowly, and this involved a drop life of 10—15 minutes. To avoid loss by evaporation during the surface-tension measurements, the orifice tube was inserted through the stopper of a small weighing bottle containing water, thereby enclosing an air space of about 8 ml.; 15 minutes were allowed

for this volume to become saturated with water vapour, and the drops were then formed at a distance of approximately 0·5 cm. from the water surface. With these precautions, drop weights were exactly reproducible.

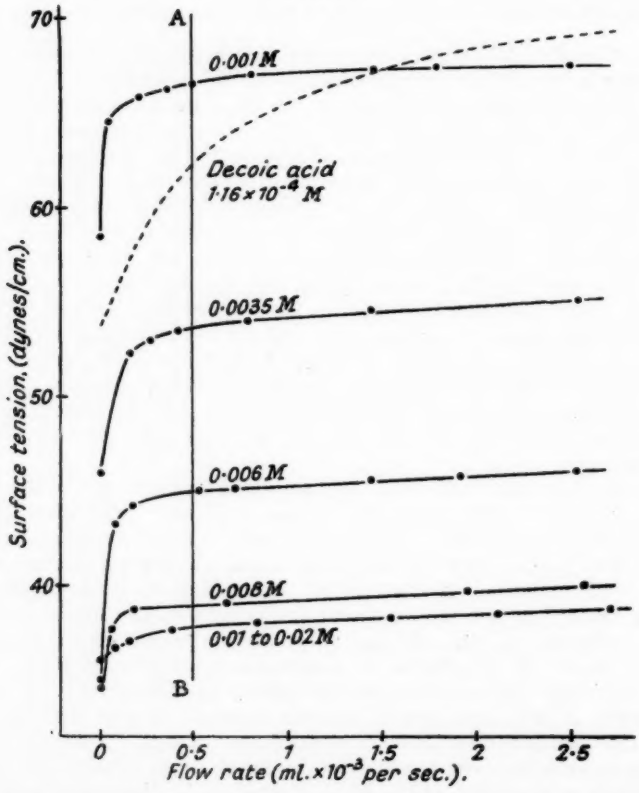
The sample of sodium dodecyl sulphate used was recrystallised several times from absolute alcohol, washed with light petroleum (b. p. 80—100°), and dried in a vacuum. Solutions were prepared in carbon dioxide-free water twice redistilled in Pyrex glass from phosphoric acid solution. The critical concentration for micelle formation in these solutions is highly sensitive to impurities; the value obtained by the vertical-plate method (0·0065M) is in close agreement with the accepted value (Powney and Addison, *loc. cit.*) and serves as a guarantee of purity.

All experiments were carried out at 15° ± 0·5°.

Discussion and Results.

The variation in the surface tensions of sodium dodecyl sulphate solution with rate of expansion of the drop is shown in Fig. 1 for concentrations in the range 0·001—0·02M. The

Fig. 1.



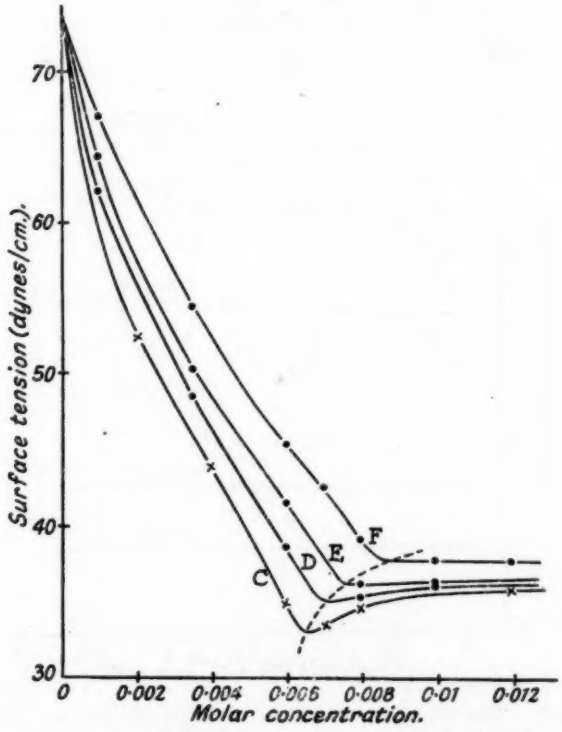
tensions at zero flow rate are those for the stationary surface as measured by the vertical plate, and the remaining tensions are determined by the expanding-drop method. The curves fall into two distinct sections divided by line *AB*, *viz.*, a rapid rise in tension immediately the surface begins to expand, followed by a slight increase (of the order of 1 dyne/cm. over the full flow-rate range), which is independent of concentration. The general shape of curve is the same for all concentrations studied, and there is no change in behaviour at the critical concentration. The following possible explanations must be considered.

(1) The surface tension of solutions of sodium dodecyl sulphate decreases with ageing of the surface. Since slow drop formation involves long drop life, the possibility arises that the lower tensions at slow flow rate may be due to this effect. However, the ageing of the surface is attributed (Alexander, *Trans. Faraday Soc.*, 1941, **37**, 15) to rearrangements in the established surface film. This is unlikely to occur at an expanding surface, and furthermore the tension values are all higher than, and fall to, the vertical-plate value determined at a fresh surface.

(2) The fall in concentration in the surface film may not be immediately replenished by

diffusion from bulk solution. However, if the time taken for replenishment of the surface is appreciable, the concentration in the surface layer depends upon the rate of surface expansion, and tension is a function of flow rate throughout the whole available flow-rate range. These conditions are known to hold for decoic acid, and a typical curve is superimposed in Fig. 1 for comparison. The dodecyl sulphate curves cannot be explained on the basis. Throughout the greater part of the flow-rate range the tension shows little change, and the γ–flow rate relation is linear. The rapid increase in γ with initial expansion of the surface would imply that the establishment of diffusion equilibrium in these solutions was slower than for decoic acid solutions whereas the vertical-plate measurements show no appreciable drift. Again, it is significant that the increase in tension on expansion is of the same order as that deduced for decoic acid solutions, where changes in tension due to diffusion have been taken into account.

FIG. 2.



Curve.	Method.	Flow rate, ml. $\times 10^{-3}$/sec.
C	*Vertical plate.*	—
D	*Drop weight.*	0·02
E	,,	0·04
F	,,	1·0

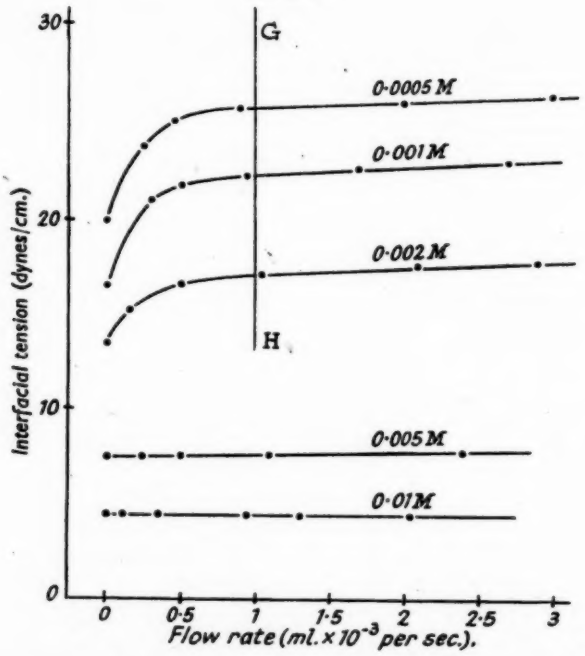
(3) Since the surface film is composed of the single long-chain ions, surface expansion may alter the distribution of electric charge at the surface. The possibility cannot yet be entirely discounted, but the fact that the increases in tension are of the same order as those deduced for decoic acid, where the surface film is composed of un-ionised acid molecules, suggests that this factor is not significant.

These curves may, however, be suitably interpreted on the basis of change in orientation. Thus the adsorbed molecules, orientated horizontally at a stationary surface in their position of highest surface activity, may be considered as being disorientated by surface expansion, so that the mean position of the carbon chains is at an angle to the surface, and in a position of lower surface activity. (Such a change in orientation should be reflected in a change in surface potential, and this aspect is being investigated.) It has been calculated in Part VIII (*loc. cit.*) that the slight expansion of a decoic acid film equivalent to a flow rate of $0{\cdot}5 \times 10^{-3}$ ml./sec. was sufficient to produce the full loss of surface activity, and Fig. 1 indicates that the initial rapid

change in tension of sodium dodecyl sulphate solutions is complete within the same narrow range of flow rate. Thus evidence is now available that soluble films of long-chain compounds terminating in the polar groups CO_2H, CO_2Na, or SO_4Na each show a change in tension of up to 10 dynes/cm. on expansion. It appears probable that the chain, rather than the polar group, is therefore responsible, and an investigation into the influence of chain length is in progress.

Tension–Concentration Curves at Stationary and at Expanding Surfaces.—The full curve relating concentration of sodium dodecyl sulphate with the surface tension at 15°, measured by the vertical plate, is shown in Fig. 2 (curve *C*). The curve is similar in position to that determined by Powney and Addison (*loc. cit.*) by the ring method, and shows a break at the same critical concentration (0·0065M). The corresponding curves for surfaces expanding at three different rates also show breaks which move to higher concentrations as the flow rate increases. Surface expansion can involve no change in the distribution of solute in bulk solution between the single ion and the micellar state, and therefore the apparent increase in critical concentration must be

FIG. 3.



a purely surface effect. The micelles contribute little to the surface activity at a stationary surface, but they may become active at an expanding surface. Again, micellar aggregation is weak, and conversion from the micellar into the single-ion state is readily achieved (*e.g.*, by dilution of the solution) so that some of the micelles which arrive at an expanding surface may be dissociated into single ions.

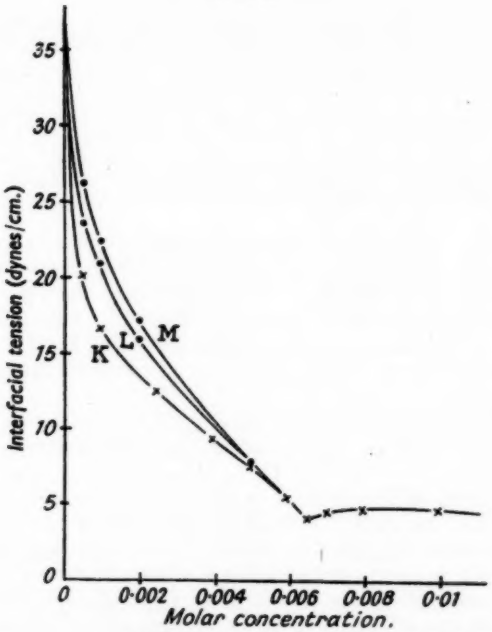
Expanding Films at Interfaces.—At the interface between water and organic liquids, the adsorbed carbon chains enter the organic liquid, and their mean position is therefore at an appreciable angle to the plane of the interface. The lowering of tension is determined by the extent to which the adsorbed molecules can form a bridge between the two phases, and this depends upon both the polar nature of the end group and the chain length. The organic liquid has an anchoring effect on the carbon chains and therefore, if the decrease in surface activity on expansion of an air–liquid interface is to be attributed to disorientation of the adsorbed molecules, the expansion of a liquid–liquid interface might be expected to influence the interfacial activity to a lesser degree.

Interfacial tensions at stationary and at expanding surfaces have been measured against toluene at 15° for a range of sodium dodecyl sulphate solutions, by the vertical-plate and the drop-volume method respectively, and the results are shown in Fig. 3. For the dilute solutions below 0·005M the curves have a shape similar to the corresponding surface-tension curves. The points at zero flow rate represent vertical-plate measurements, and a rapid rise in interfacial

tension takes place almost immediatley upon expansion of the surface, followed by a slight and uniform rise (about 1 dyne/cm.) throughout the remaining available flow-rate range. The effect disappears at concentrations beyond 0·005M, both methods of measurements then being in close agreement. At 0·005M, surface expansion changes the tension by only 0·4 dyne/cm., and at 0·01M exactly reproducible results were obtained irrespective of method or rate of surface expansion. The full interfacial tension–concentration curves are shown in Fig. 4; they show a break at the same critical concentration as for the stationary surface-tension curve in Fig. 2, but the stationary and the expanding-surface curves now coincide beyond 0·005M.

It is again possible to explain these curves on the basis of disorientation. In dilute solution the adsorbed molecules may be considered as isolated units, virtually uninfluenced by lateral cohesive forces. Owing to the attraction of the organic phase for the carbon chains, their orientation at the stationary surface will be nearer vertical than horizontal. During expansion of the interface these molecules must travel laterally, and such a molecule could only maintain its

FIG. 4.



Curve.	Method.	Flow rate, ml. × 10^{-3}/sec.
K	*Vertical plate.*	—
L	*Drop volume.*	1·0
M	,,	0·2

vertical orientation if it was so distributed across the interface that viscous and frictional resistance were equal in the two phases. The state is unlikely, since the longer carbon chains will be predominantly in the organic-liquid phase, so that the lateral motion must result in a different (and probably random) orientation at a mean angle nearer to the horizontal, with consequent decrease in the interfacial activity. The rate of surface expansion (equivalent to a flow rate of 1×10^{-3} ml./sec.) required to produce the full initial increase in tension at the liquid–liquid interface (line *GH*, Fig. 3) is twice the rate required at the air–liquid interface, and this is consistent with the anchoring effect of the toluene phase on the carbon chains. The change in orientation during lateral motion is likely to diminish as the concentration in the aqueous phase, and thus the number of adsorbed molecules, increases. It is significant that the expanding- and the stationary-surface curves (Fig. 4) only coincide at the lowest tensions; if the surface film then approaches a close-packed monolayer the lateral cohesion will resist any pronounced change in angle of orientation.

Trough Experiments.—Although the vertical-plate results (Figs. 1 and 3) clearly form the limiting points on the expanding-drop curves for zero flow rate, it seemed desirable to confirm that increase in surface tension with expansion of surface could be observed over the full tension

range when the same technique of measurement was used throughout. Solutions of sodium dodecyl sulphate were therefore placed in a trough, and the surface confined to a known area by a movable barrier. The vertical plate was then inserted into the surface, and wetted above the meniscus line to enable the plate to record increases in surface tension by entering the liquid without change of contact angle (Part VII, *loc. cit.*). On increase of the surface by means of the movable barrier, the vertical plate recorded an increase in surface tension, and preliminary experiments indicate that this increase is of the same order as those recorded in Figs. 1 and 3. When the movement of the barrier ceased, the tension decreased within a few seconds to the original value; details of these experiments will be described later.

The authors are indebted to Dr. B. D. Shaw for the sample of pure sodium dodecyl sulphate used in this work.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, June 21st*, 1947.]

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181. *Occurrence of Betulinic Acid in the Bark of the Plane Tree.*

By V. BRUCKNER, J. KOVÁCS, and I. KOCZKA.

The substance isolated from the shed bark of *Platanus acerifolia* by sublimation or extraction, m. p. 311—313° (decomp.), is identical with betulinic acid. Doubtless, "platanol" and "platanin", described by Dávid (*Magyar Gyógy. Társ. Ert.*, 1944, 8) and by Jaretzky (*Arch. Pharm.*, 1944, **282**, 75), respectively, and probably "platanolic acid", mentioned by Zellner and Ziffer (*Monatsh.*, 1925, **46**, 325), are also identical with betulinic acid.

ZELLNER and ZIFFER (*loc. cit.*) isolated from the bark of the branches of young *Platanus orientalis* a hydroxy-carboxylic acid, to which they ascribed the formula $C_{24}H_{40}O_3$, calling it "platanolic acid". They observed that it was optically inactive and showed a positive Liebermann reaction (red ⟶ violet ⟶ blue ⟶ green), and they prepared derivatives recorded in the table. Their formula was supported only by a duplicate analysis and a molecular-weight determination by Rast's method. A methoxyl determination for the methyl ester gave a very high result.

Jaretzky (*loc. cit.*) isolated from the chloroform extract of the bark of *Platanus orientalis* a very similar substance, which he called "platanin", two analyses indicating the formula $C_{30}H_{50}O_4$ or $C_{30}H_{51}O_4$ (*sic*).

Dávid (*loc. cit.*) isolated an amorphous powder from the alcoholic extract of *Platanus acerifolia* bark and obtained crystalline needles by sublimation or by extraction with absolute methanol or ethanol. This product had m. p. 304—311° (decomp.), and formed a monoacetyl derivative, m. p. 287°. From analyses and molecular-weight determinations of this substance ("platanol") and its acetate, he deduced the formula $C_{28}H_{44}O_3$ or $C_{29}H_{46}O_3$. We have isolated and investigated this "platanol" and find it to be identical with betulinic acid (prepared by Ruzicka, Lamberton, and Christie, *Helv. Chim. Acta*, 1938, **21**, 1706, by oxidising betulin monoacetate), which was discovered shortly afterwards in the bark of *Cornus florida* (Robertson, Soliman, and Owen, *J.*, 1939, 1267) and in the seeds of *Zyzyphus vulgaris* (Kavaguchi and Kim, *J. Pharm. Soc. Japan*, 1940, **60**, 171).

Our conclusions are based on the following experimental data (see also table): (1) The physical constants, properties, and colour reactions of platanol are identical with those of betulinic acid; *e.g.*, pure platanol melts at 311—313° (decomp.), shows a positive Liebermann reaction (red ⟶ violet ⟶ blue ⟶ green), and is optically active ($[\alpha]_D^{22°}$ + 7·79° in pyridine). (2) Several analyses of platanol and its derivatives, and determination of molecular weights, especially the equivalent, support the formula $C_{30}H_{48}O_3$. (3) Platanol contains an easily acetylated hydroxyl group, and the acetate has m. p. 287—289°, regenerating the original substance on hydrolysis. (4) The presence of a carboxyl group in platanol was proved by titration in alcoholic solution and by esterification with diazomethane. (5) Platanol is unsaturated (yellow colour with tetranitromethane) and readily forms a dihydro-derivative, which can be acetylated and then esterified. (6) The hydroxyl group is secondary, since the dihydro-derivative can be oxidised to a ketone, forming an *oxime*. (7) Platanol yielded on bromination in chloroform solution at room temperature a *monobromo*-derivative, m. p. 250—251°. Although Robertson *et al.* (*loc. cit.*) found the bromination product of betulinic acid to be an "unseparable mixture of different bromo-derivatives", our substance was homogeneous, analysis being accurate for $C_{30}H_{47}O_3Br$. (This discrepancy is probably due to the different methods

used in the bromination.) The bromo-derivative forms an acetyl derivative, m. p. 280°, identical with that obtained by brominating the above acetate. This m. p. is 10° lower than that for the compound prepared by Robertson *et al.* (*loc. cit.*) by bromination of acetylbetulinic acid in ether–glacial acetic acid solution, but our product is not a lactone, for it gives acid reactions in alcoholic solution and can be esterified with diazomethane. (8) The isomeric lactone acetate, m. p. > 340°, results on treating platanol with glacial acetic acid–hydrochloric acid, or by various other methods. (9) M. p.s (and optical activity determined in several cases) of the platanol derivatives agree with those recorded for the corresponding derivatives of betulinic acid. (10) Selenium dehydrogenation yielded 1 : 2 : 5 : 6-tetramethylnaphthalene and a saturated hydrocarbon (not investigated, see Experimental).

We therefore conclude that " platanol " is identical with betulinic acid. Doubtless, Jaretzky's " platanin " (*loc. cit.*) is the same compound: his low analytical values can be explained by the fact that it readily retains small amounts of solvent. Zellner and Ziffer's " platanolic acid " too is probably the same as " platanol ", for it agrees in all its properties and reactions, and the m. p.s of their derivatives (except the bromo-compound) would have approximated to ours if they had been corrected, especially as betulinic acid slowly decomposes above 280°; moreover, their analyses are not in good agreement with the formula $C_{24}H_{40}O_3$, and our analyses of *impure* " platanol " agreed with theirs. Their statement that " platanolic acid " is optically inactive is not of much significance, for the specific rotatory power of betulinic acid is very low.

*Melting points of betulinic acid, platanol, platanolic acid, platanin, and their derivatives.**

	Betulinic acid.	Platanol (this paper).	Platanolic acid.	Platanin.
(I) Original substance	316—318° [b]	311—313°	281° [f]	313—315° [g]
	315—317 [c]			321—323 [g]
(II) Acetyl deriv.	288—290 [a]	287—289	277 [f]	—
	281—291 [b]			
(III) Dihydro-deriv.	323—324 [a]			
	316—320 [b]	311—315	—	—
	317—319 [c]			
(IV) Acetyldihydro-deriv.	311—312·5 [d]			
	307—310 [b]	307	—	—
	308—310 [c]			
(V) Keto-dihydro-deriv.	256—257 [a, d]	255—258	—	—
(VI) Oxime of (V)	—	285	—	—
(VII) *Acetate* of (VI)	—	150—151	—	—
(VIII) Methyl ester of (I)	224—225 [a]	224—225	214—215 [f]	—
	223—224 [b]			
(IX) Methyl ester of (II)	200—202 [a]	203	—	—
	201—202 [b]			
(X) Methyl ester of (IV)	238·5—239 [a, e]	235	—	—
	237—239 [c]			
(XI) Monobromo-deriv. of (I)	—	250—251	211 [f]	—
(XII) Monobromo-deriv. of (II)	290 [b]	280	—	—
(XIII) *Methyl* ester of (XII)	—	138—140	—	—
(XIV) Lactone acetate	> 350 [b]			
	357—360 [b]	> 340	—	—
	344—346 [c]			

* M. p.s are corrected, except those of platanolic acid and its derivatives.

(*a*) Ruzicka, Lamberton, and Christie, *loc. cit.*
(*b*) Robertson, Soliman, and Owen, *loc. cit.*
(*c*) Kawaguchi and Kim, *loc. cit.*
(*d*) *Idem*, *ibid.*, p. 235.
(*e*) Ruzicka, Brenner, and Rey, *Helv. Chim. Acta*, 1941, **24**, 515.
(*f*) Zellner and Ziffer, *loc. cit.*
(*g*) Jaretzky, *loc. cit.* The first m. p. was obtained by rapid heating, and the second by using a Berl block preheated at 310°.

Experimental.

(Melting points are corrected.)

Isolation.—The bark (2000 g.) of *Platanus acerifolia* (shed in spring) was cut into small pieces and extracted for 9 hours with methanol (5·5 l.). The extract was concentrated to 500 ml. and cooled; the substance crystallised, and was filtered off, washed with cold methanol, and dried (36 g.). The dirty-green product, recrystallised from absolute methanol (charcoal), afforded colourless needles (14 g.). For analysis, it was recrystallised 5 times from absolute methanol, and dried at 130° in a vacuum; m. p. 311—313° (decomp.), $[\alpha]_D^{22°}$ + 7·79° in pyridine (Found: C, 78·6, 78·9; H, 10·4, 11·0. Calc. for

$C_{30}H_{48}O_3$: C, 78·85; H, 10·6%). The substance further purified through the acetate (below) gave: C, 78·8, 78·9, 78·8; H, 10·8, 10·7, 10·8; *M* (Rast), 451·8; *M* (by titration), 460·9 (Calc.: *M*, 458·7).

Acetate (II).—Platanol (2 g.) was dissolved in boiling acetic anhydride (10 ml.) or boiled for a short time with glacial acetic acid. The product precipitated by cooling was recrystallised from methanol. For analysis it was dried for 4 hours at 130° in a vacuum; m. p. 287—289° (decomp.), $[\alpha]_D^{25°}$ + 12·09° in pyridine [Found: C, 76·8, 77·2; H, 10·1, 10·0; *M* (ebullioscopic), 497·5; *M* (by titration), 498·2. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%; *M*, 498·7). When this acetate (2 g.) was boiled with 10% methanolic potash (35 ml.) for 30 minutes, and then acidified, the product, recrystallised from absolute methanol, was identical with the original substance [m. p., mixed m. p., and analysis (see above)].

Acetyldihydrobetulinic Acid (IV).—This was prepared (*a*) by hydrogenation in presence of a platinum oxide catalyst of a solution of platanyl acetate (1 g.) in absolute ethanol (300 ml.) or ethyl acetate (40 ml.), and (*b*) by boiling dihydroplatanol (III) (0·5 g.) with anhydrous acetic acid (10 ml.). Crystallised from methanol or glacial acetic acid, it yields colourless plates, m. p. 307° (decomp.) (Found: C, 76·65, 76·85, 77·0; H, 10·5, 10·5, 10·5. Calc. for $C_{32}H_{52}O_4$: C, 76·75; H, 10·5%).

Dihydrobetulinic Acid (III).—Pure platanol (1 g.), dissolved in ethanol (500 ml.), was shaken in an atmosphere of hydrogen in the presence of prehydrogenated platinum oxide (0·3 g.). Absorption of 1 mol. of hydrogen was complete in 60 minutes. The solution was concentrated, and the substance crystallised. It retains ½ mol. of ethyl alcohol even after drying at 140° in a vacuum (Found: C, 77·3, 77·2, 77·1; H, 11·2, 10·9, 10·9. Calc. for $C_{30}H_{50}O_3,\frac{1}{2}C_2H_6O$: C, 77·3; H, 11·1%), which it loses on drying at 200° (Found: C, 78·35; H, 11·05. Calc. for $C_{30}H_{50}O_3$: C, 78·55; H, 11·0%); m. p. 311—315° (decomp.). Unlike the original substance, this shows no colour reaction with tetranitromethane.

Dihydrobetulonic Acid (V).—To a solution of dihydroplatanol (1 g.) in glacial acetic acid (80 ml.) a solution of chromic acid (0·23 g.) in glacial acetic acid was added, and the whole warmed on a steam-bath for 60 mins. The solution was then evaporated, and the residue digested with water, filtered off, and dried. Recrystallised from acetone, it yielded delicate needles, m. p. 255—258° (decomp.) (Found: C, 78·7, 78·55; H, 10·7, 10·9. Calc. for $C_{30}H_{48}O_3$: C, 78·85; H, 10·6%).

Oxime (VI). The substance (V) (0·4 g.) was dissolved in ethanol and an alcoholic solution of hydroxylamine hydrochloride (0·05 g.), and a 2% alcoholic solution of potassium hydroxide (2 ml.) was added. After 24 hours the precipitated *oxime* was recrystallised from ethanol; needles, m. p. 285° (decomp.) (Found: C, 76·5, 76·25; H, 10·5, 10·55. $C_{30}H_{49}O_3N$ requires C, 76·4; H, 10·5%). The oxime (100 mg.) was boiled with acetic anhydride (5 drops), and the product cooled and mixed with excess of saturated potassium carbonate solution; the precipitated *acetate* (VII), crystallised from 70% ethanol and dried at 70° in a vacuum, had m. p. 150—151° (Found: C, 74·3, 74·0; H, 10·2, 10·5. $C_{32}H_{51}O_4N$ requires C, 74·5; H, 10·4%).

Methyl Betulinate (VIII).—Platanol (2 g.) was dissolved in methanol (350 ml.), and an ethereal solution of diazomethane added at 0°. The ester was precipitated on concentration of the solution; recrystallised from benzene (10 ml.), it formed colourless prisms, m. p. 224—225° (Found: C, 79·3; H, 10·8. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%).

Methyl Acetylbetulinate (IX).—This was prepared from (II) (0·5 g.) by means of diazomethane. Recrystallised from methanol, and dried at 100° in a vacuum, it yielded small prisms, m. p. 203°, $[\alpha]_D^{15°}$ + 16·86° in chloroform (Found: C, 77·7; H, 10·3. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2%).

Methyl Acetyldihydrobetulinate (X).—The acetyl compound (IV) (0·2 g.) was dissolved in methanol (40 ml.) and treated with diazomethane. The crystalline substance obtained by concentrating the solution was recrystallised from methanol and dried at 100° in a vacuum, affording prisms, m. p. 235° (Found: C, 76·85; H, 10·65. Calc. for $C_{33}H_{54}O_4$: C, 77·0; H, 10·6%).

Bromobetulinic Acid (XI).—To a solution of platanol (2 g.) in cold chloroform a 4% chloroform solution of bromine (0·7 g.) was added in small portions. After separation of a small gelatinous precipitate, the solution was concentrated under reduced pressure at room temperature until crystallisation took place. The substance was filtered off, washed with ice-cold chloroform, and dried over paraffin in a vacuum at room temperature; colourless needles, m. p. 250—251° (decomp.) (Found, for crude substance: C, 67·1, 67·5; H, 8·6, 8·7. Found, for substance recrystallised from benzene, and dried at 60° in a vacuum: C, 67·5; H, 8·7. $C_{30}H_{47}O_3Br$ requires C, 67·3; H, 8·8%).

Acetylbromobetulinic Acid (XII).—(*a*) The foregoing substance (XI) was boiled with excess of acetic anhydride, and the precipitated acetyl derivative recrystallised from ligroin. (*b*) Platanol (1·6 g.) was dissolved in boiling glacial acetic acid (100 ml.), cooled to 40°, and a solution of bromine (0·6 g.) in glacial acetic acid added. The resulting solution was concentrated under reduced pressure, and the residue dried for 24 hours over potassium hydroxide in a vacuum at room temperature and finally recrystallised from benzene. (*c*) Substance (II) (1 g.) was dissolved in cold chloroform (20 ml.) and a 4% solution of bromine (0·35 g.) in chloroform was added. After evaporation at room temperature under reduced pressure, the residue was dissolved in a small amount of chloroform and diluted with 6—7 vols. of methanol; the substance crystallised in analytically pure state. The three products were identical; m. p. 280° (decomp.) [Found: (*a*) C, 66·6; H, 8·6; (*b*) C, 66·4, 66·5; H, 8·65, 8·9; (*c*) C, 66·3, 66·6; H, 8·7, 9·0. Calc. for $C_{32}H_{49}O_4Br$: C, 66·5; H, 8·55%].

Methyl Acetylbromobetulinate (XIII).—The foregoing substance (XII) (0·15 g.) was dissolved in cold methanol (20 ml.), and a solution containing 0·5 mol. of diazomethane (10 ml.) added at 0°. Concentration of the solution afforded a crystalline *ester*, which was recrystallised from methanol, and dried at 80° in a vacuum, giving delicate needles, m. p. 138—140° (Found: C, 66·5; H, 9·0. $C_{33}H_{51}O_4Br$ requires C, 67·0; H, 8·7%).

Acetylbetulinic Acid Lactone (XIV).—(*a*) Platanol (2 g.) was boiled with 98% formic acid (70 ml.). The greater part dissolved at first and then afforded a precipitate. Recrystallised from xylene, this yielded long needles, m. p. 330° (decomp.), which did not react with diazomethane or with bromine. As the analyses for this product were not satisfactory it was converted into its acetyl derivative by means of acetic anhydride, and this was recrystallised from xylene, yielding needles, m. p. > 340° (decomp.). (*b*) Substance (II) (1·5 g.) was boiled with 98% formic acid for 1 hour; the crystals which separated on cooling were washed with water, dried (1·1 g.), boiled with benzene (10 ml.), and recrystallised from

xylene, yielding needles, m. p. > 340° (decomp.). (*c*) Powdered platanol (5 g.) was heated with glacial acetic acid (35 ml.) containing 10% of hydrogen chloride for 90 minutes at 100° in a sealed tube. Water (70 ml.) was added, and the precipitate was washed with water, dried, and boiled for 10 minutes with acetic anhydride (60 ml.). The substance precipitated on cooling was boiled with benzene (40 ml.) and finally recrystallised from xylene; needles, m. p. > 340° (decomp.). (*d*) Powered platanol (5 g.) was refluxed with a mixture of glacial acetic acid (150 ml.) and hydrochloric acid (*d* 1·19; 150 ml.) for 2 hours. Only part dissolved, and the residue was filtered off; the filtrate was diluted with water (300 ml.), and the precipitate washed with water, dried, boiled with benzene, and recrystallised finally from xylene; needles, m. p. > 340° (decomp.). (*e*) Into a solution of platanol (1 g.) in ether–ethanol (2 : 1; 300 ml.), dry hydrogen chloride was passed for 2 hours. Concentration of the solution to 70 ml. precipitated an amorphous product, which was acetylated with acetic anhydride. The product crystallised from xylene in needles, m. p. > 340° (decomp.) [Found: (*a*) C, 76·9; H, 10·2; (*b*) C, 77·2; H, 10·3; (*c*) C, 77·1; H, 10·3. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%].

Dehydrogenation of Platanol.—Platanol (30 g.) was heated in an atmosphere of nitrogen in a metal-bath to 240°, selenium (17 g.) was added, and the temperature increased to 265°; more selenium (7 g.) was then added and the temperature increased during 40 minutes to 335°. Evolution of hydrogen selenide began at 310°. After 1½, 2½, and 8 hours further portions of selenium (7 g.) were added, and heating was continued for another 30 hours at 335—340°. The dark residue was cooled and extracted with ether (250 ml.), and the extract filtered and evaporated. A dark brown fluorescent oil (24 g.) remained, which was fractionated under reduced pressure: (1) <120°/17 mm., 0·15 g. of lemon-yellow oil; (2) 120—140°/4 mm., 5·6 g. of yellow oil; (3) 140—240°/4 mm., 0·2 g. of brown oil which crystallised; (4) > 240°/4 mm., 1·0 g. of brown oil solidifying to a glass. Only fractions (2) and (3) were investigated.

Fraction (2). This was dissolved in absolute ethanol (15 ml.), and a solution of picric acid (2 g.) in ethanol (20 ml.) added. The red solution thus obtained was boiled for 10 minutes, then evaporated, and the residue collected on a fritted-glass filter and washed with cold ethanol. The crude picrate (2·4 g.) was recrystallised from absolute ethanol (20 ml.), yielding red needles (1·6 g.), m. p. 134—135°, raised by another six crystallisations to 143°, and by a seventh to 148° (Found: C, 58·0; H, 4·5; N, 10·2. Calc. for $C_{20}H_{18}O_7N_3$: C, 58·1; H, 4·6; N, 10·2%). Ruzicka *et al.* (*Helv. Chim. Acta*, 1933, **16**, 320) give m. p. 154—154·5° for pure 1 : 2 : 5 : 6-tetramethylnaphthalene picrate.

One part of the crude picrate, m. p. 134—135°, was treated with dilute ammonia, and the regenerated hydrocarbon was crystallised from ethanol and dried in a vacuum at 50—60°, forming colourless needles, m. p. 111—112° (Found: C, 91·5; H, 8·9. Calc. for $C_{14}H_{14}$: C, 91·25; H, 8·75%). As Ruzicka *et al.* (*loc. cit.*) give m. p. 116° for 1 : 2 : 5 : 6-tetramethylnaphthalene, we assume that our substance was a not quite pure specimen of this hydrocarbon.

Fraction (3). Dissolved in hot absolute ethanol (20 ml.), this yielded on cooling a small amount of colourless needles which, recrystallised from methanol, formed needles, m. p. 44—45°. The substance was saturated, for it gave no reaction with picric acid, showed no colour reaction with tetranitromethane, and did not discolour a solution of potassium permanganate or bromine. Analyses agreed with that for a C_{30} paraffin or a saturated hydrocarbon C_nH_{2n}. Molecular-weight determination (Rast) gave values between 420 and 480. We think it very improbable that by dehydrogenation a paraffin of this high carbon number could be obtained, but lack of material prevented further investigation (Found: C, 85·0, 85·6, 85·3; H, 14·6, 14·5, 14·7. Calc. for $C_{30}H_{62}$: C, 85·2; H, 14·8%. Calc. for C_nH_{2n}: C, 85·6; H, 14·4%).

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182. *Strychnine and Brucine. Part L. Experiments with Pseudostrychnine, Dihydropseudostrychnine, and* neo*Strychnine.*

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Pseudostrychnine (hydroxystrychnine) condenses with nitromethane to *nitromethylstrychnine* and with *p*-nitrophenylhydrazine and 2 : 4-dinitrophenylhydrazine to substituted *arylhydrazones* of *sec.*-pseudostrychnine.

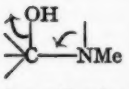
*neo*Strychnine is reduced by zinc and dilute hydrochloric acid to dihydrostrychnine under conditions whereby strychnine remains unchanged. *neo*Strychnine combines with acetic anhydride with formation of a neutral *product*, $C_{23}H_{24}O_5N_2$.

Dihydropseudostrychnine methyl ether is converted by Raney nickel in boiling xylene into *neo*strychnine. In the same way pseudostrychnine methyl ether yields a *hydroxyneostrychnine* (or possibly a homologue, see below) reduced by zinc and hydrochloric acid or by catalytic hydrogenation to a new x-*hydroxydihydrostrychnine* (or a homologue). The latter base is changed by Raney nickel into *neo*strychnine. Pseudostrychnine reacts with phosphorus trichloride, and the *product*, isolated after solution in aqueous ammonia and acidification, has the composition $C_{21}H_{23}O_5N_2P$. This is a very stable substance, unaffected by hot dilute acids and alkalis. It does not form a hydrochloride but yields an abnormal *perchlorate*, $2C_{21}H_{22}O_5N_2P,HClO_4,H_2O$. On catalytic reduction it absorbs four atoms of hydrogen.

*neo*Strychnine (but not strychnine) reacts with phosphoric acid and with phosphorous acid to form *substances* $C_{21}H_{23}O_5N_2P$ and $C_{21}H_{27}O_6N_2P$ (probably $C_{21}H_{23}O_4N_2P,2H_2O$) respectively. Each of these absorbs two atoms of hydrogen on catalytic reduction. The nature of these substances is not clear but they are possibly substituted amides of phosphoric and phosphorous acids.

THE pseudostrychnine of Warnat (*Helv. Chim. Acta*, 1931, **14**, 997) had m. p. 268° (decomp.), and the work of Blount and Robinson (*J.*, 1932, 2307) was carried out with material of the same Swiss origin. Leuchs and Räck (*Ber.*, 1940, **73**, 734), following Leuchs (*Ber.*, 1937, **70**, 1543) and Leuchs and Tessmar (*ibid.*, p. 2369), oxidised strychnine by atmospheric oxygen in the presence of Fehling's solution and obtained an isomeride, m. p. 233°. This was stated to be convertible into Warnat's pseudostrychnine by simple solution in dilute hydrochloric acid and precipitation with ammonia. Nevertheless it was found (Leuchs, Grünow, and Tessmar, *Ber.*, 1937, **70**, 1701) that the isomeride, m. p. 233°, was more resistant to catalytic hydrogenation in acid solution than that of m. p. 263°, though the same dihydro-derivative was obtained. This suggests a slow transformation and reduction by way of the substance of m. p. 263°. On these grounds as well as from the different rotatory powers there seems to be little doubt but that the isomerism is real. Unfortunately we do not yet know whether the underlying cause is stereochemical or structural and it may be a source of confusion that many experiments on pseudostrychnine have been recorded without any statement of the m. p. of the material employed.

The base employed in the present investigations had m. p. 235° and was prepared by the method of Leuchs and Räck (*loc. cit.*) before that described in the previous part of this series (Bailey and Robinson, this vol., p. 703) had been discovered. The condensation reactions of pseudostrychnine on the one hand, and its conversion into derivatives of *sec.*-pseudostrychnine (such as the neutral *N*-nitroso- and *N*-acetyl derivatives) on the other, show that the base is a typical carbinol-amine, ·C(OH)·N·, and it is thus an analogue of cotarnine. Yet there are contrasts : as one example, cyanohydrocotarnine is easily decomposed into its generators by mineral acids, but cyanodihydrostrychnine is very stable to hot hydrochloric acid. These divergences do not obscure the general correspondence of reaction type and are probably due to the circumstance that the stereochemical configuration of pseudostrychnine does not permit a large displacement from the carbinol-amine to the unsaturated quaternary ammonium structure. The arrows in the annexed expression may represent the full transfer of two electrons in cotarnine, but it is now suggested that only a small fraction of such a transfer is possible in the pseudostrychnine molecule. The hypothesis of small alternating displacements allows us to envisage a reaction mechanism in such a case which is fully analogous to that postulated when a large displacement may be assumed.



Hope and Robinson found that cotarnine condensed with the greatest readiness with nitromethane, 2 : 4-dinitrotoluene, and 2 : 4 : 6-trinitrotoluene in alcoholic solution (*J.*, 1911, **99**, 2114). Pseudostrychnine undergoes no condensation under these conditions, doubtless because the ethyl ether is formed and is much less reactive than the corresponding derivative of cotarnine. The condensation of pseudostrychnine with nitromethane, used also a solvent, occurs, however, and the product is *anhydropseudostrychninenitromethane*.

Although the imino-group of *sec.*-pseudostrychnine has been recognised by the preparation of *N*-substituted derivatives, the carbonyl group of this substance has hitherto not been directly characterised.

We now find that the p-*nitrophenylhydrazone* and the 2 : 4-*dinitrophenylhydrazone* can be obtained.

N-*Acetyl*-sec.-*pseudostrychnine* also affords a p-*nitrophenylhydrazone*. Hydrolysis of *N*-acetyl-*sec.*-pseudostrychnine by means of hot dilute hydrochloric acid gives pseudostrychnine.

Interesting results were obtained in studying the action of Raney nickel on pseudostrychnine derivatives. Dihydropseudostrychnine methyl ether is better obtained by hydrogenation of pseudostrychnine methyl ether in the presence of platinic oxide than by the method of Leuchs and Räck (*Ber.*, 1940, **73**, 811) which depended on reduction of pseudostrychnine followed by condensation with methanol. Reversal of the order of the processes avoids the formation of strychnine by hydrogenolysis.

When dihydropseudostrychnine methyl ether was refluxed with Raney nickel in xylene, *neo*strychnine was produced in good yield. This result does not demonstrate a close structural relation between the two substances as, for example, in the formation of a double bond by simple elimination of methanol, though it is clearly consistent with that hypothesis. Similar treatment of pseudostrychnine methyl ether furnished a base, the analyses of which point to the formula $C_{22}H_{24}O_3N_2$, though $C_{21}H_{22}O_3N_2$ is not definitely excluded. But the base does not contain a methoxyl group or a methylimino-group, and if methyl were attached to carbon the eventual transformation to *neo*strychnine would be hard to explain. For these reasons the formula $C_{21}H_{22}O_3N_2$ must be entertained, and we regard the base provisionally as x-*hydroxy*neo*strychnine*. The *neo*-double-bond character is evinced by the behaviour on coupling with *p*-nitrobenzenediazonium chloride in acid solution.

On catalytic reduction, a volume of hydrogen corresponding to two atoms is absorbed, and the product is $C_{21}H_{24}O_3N_2$ ($C_{22}H_{26}O_3N_2$?). The same substance is obtainable by reduction with zinc and dilute hydrochloric acid, and it is noteworthy that *neo*strychnine (but not strychnine) can be reduced to dihydrostrychnine in the same way. This is even a convenient method of preparation of dihydrostrychnine. The reduced base, $C_{21}H_{24}O_3N_2$, is tentatively considered to be *x-hydroxydihydrostrychnine*. On treatment with Raney nickel in boiling xylene, it was converted into *neo*strychnine.

The base $C_{21}H_{24}O_3N_2$ is not identical with the isomeric dihydropseudostrychnine and hence the position *x* may denote one of the carbon atoms of the strychnine double bond. If that supposition is justified the substance might be a primary or secondary alcohol, and another isomeride, which has been isolated and which will be described in the next part of the series, comes into consideration for the former possibility. Its properties are quite different from those of *x*-hydroxydihydrostrychnine. Furthermore *neo*strychnine is now known (see Part LI) to contain the group $\therefore N(b)\cdot CH{=}C\therefore$, and hence the *x*-hydroxy*neo*strychnine cannot be formulated with a hydroxyl group on the β-carbon atom. As it is clearly improbable that a hydroxyl group has been introduced into some position unrelated to the strychnine unsaturation, the most plausible hypothesis is that *x*-hydroxy*neo*strychnine contains the group $\therefore N(b)\cdot CH{=}\overset{|}{C}\cdot CH(OH)\cdot CH_2$. We know that an oxidation–reduction process may involve the two carbon atoms joined to N(b), and hence the mechanism may be: $\therefore C(OH)\cdot \dot{N}(b)\cdot CH_2\cdot \dot{C}{=}CH^- \longrightarrow \therefore CH\cdot \dot{N}\cdot CH(OH)\cdot \dot{C}{=}CH^- \longrightarrow \therefore CH\cdot \dot{N}\cdot CH{=}\dot{C}\cdot CH(OH)\cdot$, the last step by allyloid rearrangement.

Attempts to bring about a ring-fission of *neo*strychnine, $\therefore N{-}CH{=}C\therefore \longrightarrow \therefore NH\ CHO\cdot CH\therefore$, have been continued, but the system shows unusual stability. Failure with acids under varied conditions has already been reported. In the presence of hydroxylamine or *p*-nitrophenylhydrazine some indications of hydrolysis have been obtained and the same is true of the Schotten–Baumann benzoylation. A definite reaction with formation of a neutral product occurs on long treatment with acetic anhydride at 100°. The base adds the elements of the reagent and the product may contain $\therefore N(b)\cdot COMe\ Me\cdot CO\cdot O\cdot CH{=}C\therefore$. Its investigation has not yet been completed. In the course of the benzoylation experiments the formation of much benzoic anhydride was noted. It was then found that benzoic anhydride can be prepared by shaking benzoyl chloride with aqueous sodium hydroxide in the presence of quite small quantities of pyridine. The method is convenient for the preparation of the anhydrides of aromatic acids.

An attempt to dehydrate pseudostrychnine by means of phosphorus trichloride led to the eventual formation of an acidic *substance*, $C_{21}H_{23}O_5N_2P$, which was at first thought to be a phosphinic acid. It is now regarded as a phosphinamide: $\therefore N(b)\cdot C(OH)\therefore \longrightarrow \therefore N\cdot PO_2H\ CO\therefore$. The four hydrogen atoms absorbed on catalytic reduction are presumably taken up by the carbonyl group and the strychnine double bond. The carbonyl group could not be detected by the formation of derivatives.

*neo*Strychnine affords similar *products* with both phosphorous and phosphoric acids. These furnish *dihydro*-derivatives ($CHO \longrightarrow CH_2\cdot OH$?), and the power to form *p*-nitrophenylhydrazones (colour-reaction test) is lost after the reduction. All attempts to hydrolyse these substances were unsuccessful. A curious point in regard to the product from *neo*strychnine and phosphoric acid is that it has the composition $C_{21}H_{23}O_5N_2P$ and not the expected $C_{21}H_{25}O_6N_2P$ (for $N\cdot CH{=}C \longrightarrow NPO_3H_2$, $CHO\cdot CH$). The Otto reaction is exhibited [N(a)·CO present] and loss of the cyclic ether oxygen is unlikely; hence the groups present may be $\therefore N(b)\cdot PO_2$, $CHO\cdot CH\therefore$ or $\therefore N(PO_2H)\cdot O\cdot CH\therefore C\therefore$.

Of miscellaneous observations the following may be mentioned. (*a*) Kotake, Sakan, and Kusumoto (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1939, **35**, 415) found that the action of ozone on strychnine furnished pseudostrychnine.

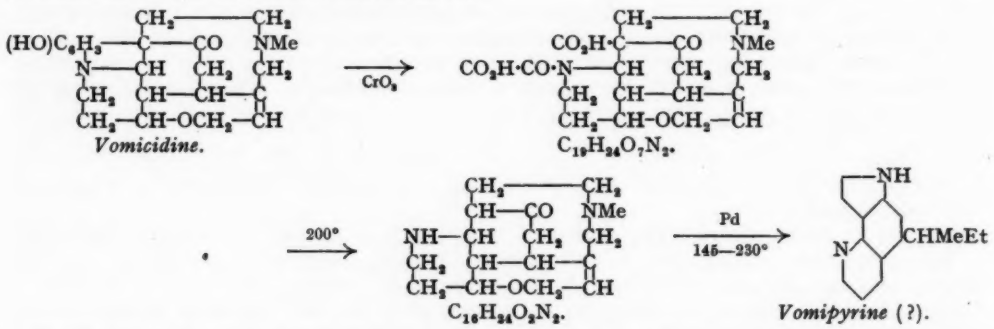
Ozonisation of *neo*strychnine, however, affords the neutral ketone, $C_{21}H_{22}O_4N_2$, first prepared by Kotake and Yokayama (*ibid.*, 1937, **31**, 329) by oxidation of *neo*strychnine with permanganate.

(*b*) A *dibenzylidene* derivative (+ H_2O) can be obtained from strychninonic acid. Doubtless one benzylidene group is vicinal to N(a)·CO·, but it is not probable that the second indicates a methylene group adjacent to the carbonyl. It may well be that the groups introduced are $\therefore N(a)\cdot CO\cdot C(\therefore CHPh)\cdot$ and $\therefore N(b){-}CHPh{-}\dot{C}{-}CO\cdot CO_2H$. This theory involves hydrolysis of the α-keto-amide structure and is thus H_2O more than a dibenzylidene derivative; the ring bridged by the benzylidene group would be five-membered.

(*c*) Some years ago, one of us suggested to Professor H. Wieland that vomicine is constituted

like *N*-methylchanopseudostrychnine (*N*-methyl-*sec.*-pseudostrychnine) with, of course, a phenolic hydroxyl group in the *o*-position to N(a).

That hypothesis was rejected by Professor Wieland (letter dated May 15th, 1939),* but it still seems much more probable than the view advanced by him that vomicine contains $-O\cdot CH_2\ N(b)\!:$. All experience shows that such acetal-like structure are readily hydrolysed by acids. Since the extra carbon atom is analytically recognisable as present in NMe, the Wieland hypothesis is the only good alternative to the preferred postulation of an actual NMe in vomicine. The additional oxygen must then be in a carbonyl or cyclic ether group; the latter theory introduces many difficulties, but the former is feasible on account of the weak carbonyl character and the stability of *N*-methyl-*sec.*-pseudostrychnine. This view also provides a ready explanation of the facile decarboxylation of certain carboxylic acids (such as the intermediate for vomipyrine) obtained by the oxidative degradation of the aromatic nucleus (Wieland and Horner, *Annalen*, 1937, **528**, 73).



It should be further noted that the acid $C_{19}H_{24}O_7N_2$ probably exists in a betaine form, $CO_2^-\cdot\dot{C}\cdot\dot{C}(OH)\cdot\dot{N}Me^+$ (second line from the top of the formula), and thus would neither exhibit carbonyl reactions nor be so unstable as a normal β-ketonic acid.

Experimental.

Pseudostrychnine, m. p. 235°, was used throughout (Found : C, 71·8; H, 6·3; N, 8·2. Calc. for $C_{21}H_{22}O_2N_2$: C, 72·0; H, 6·3; N, 8·0%); it was prepared by the method of Leuchs and Räck (*loc. cit.*).

Anhydropseudostrychninenitromethane.—A mixture of pseudostrychnine (0·5 g.) and nitromethane (10 c.c.) was heated for 3 hours on the steam-bath. The excess of nitromethane was evaporated under diminished pressure and the residue crystallised from aqueous alcohol; the *compound* formed pale yellow needles, m. p. 170° with frothing (Found : C, 65·7; H, 6·1. $C_{22}H_{23}O_4N_3,0{\cdot}5H_2O$ requires C, 65·7; H, 6·0%).

sec.-*Pseudostrychnine* p-*Nitrophenylhydrazone.*—A mixture of pseudostrychnine (0·35 g.), *p*-nitrophenylhydrazine (0·15 g.), and pyridine (3 c.c.) was refluxed for 1½ minutes. The tar precipitated by water gave crystals from aqueous alcohol. After several recrystallisations (charcoal) the fine yellow needles had m. p. 235° (Found : C, 67·1; H, 6·0. $C_{27}H_{27}O_4N_5$ requires C, 66·8; H, 5·6%). The alcoholic solution developed a crimson coloration on the addition of sodium hydroxide. The p-*nitrophenylhydrazone* is stable towards yellow mercuric oxide in boiling alcoholic solution.

The corresponding 2 : 4-*dinitrophenylhydrazone* was prepared in a like fashion. It formed orange needles, m. p. 166° (decomp.) (Found : C, 58·8; H, 4·9. $C_{27}H_{26}O_6N_6,H_2O$ requires C, 59·1; H, 5·1%). This derivative was also not oxidisable by means of mercuric oxide.

N-*Acetyl*-sec.-*pseudostrychnine.*—The crude substance (0·51 g.) was refluxed for 1·25 minutes with *p*-nitrophenylhydrazine (0·15 g.) in acetic acid (2 c.c.). The *product* crystallised from aqueous alcohol (charcoal) as slender, light yellow needles, m. p. 187° (decomp.) (Found : C, 63·4; H, 5·6. $C_{23}H_{29}O_5N_5,H_2O$ requires C, 63·8; H, 5·7%). The alcoholic alkali colour reaction was the same as that of the *p*-nitrophenylhydrazone of pseudostrychnine. *N*-Acetylpseudostrychnine (0·5 g.) was hydrolysed by means of boiling 2N-hydrochloric acid (20 c.c.). 0·4 G. of pseudostrychnine, m. p. 235°, was obtained on basification of the filtered solution with ammonia. The m. p. was not depressed on admixture with an authentic specimen.

Dihydropseudostrychnine Methyl Ether.—Pseudostrychnine methyl ether (2·0 g.), m. p. 191·3°, was hydrogenated in methanol (100 c.c.) at the ordinary temperature and pressure in the presence of platinic oxide (0·1 g.). 152 C.c. of hydrogen (calc., 143 c.c.) were absorbed. Concentration of the filtered solution gave the dihydro-derivative (2·0 g.), m. p. 196—199°, and 197—199° when mixed with a specimen, m. p. 198—199°, prepared according to Leuchs (*loc. cit.*).

A mixture of this substance (0·6 g.), Raney nickel sediment (1·3 c.c.), and xylene (80 c.c.) was distilled

* *Added June 18th*, 1948.—Professor Wieland has now concurred in the vomicine formula, and a joint communication on vomicine chemistry is in preparation. He has disclosed that vomipyrine contains NMe, and hence the formula suggested must be modified to contain NMe in the pyrrole ring, and also *iso*butyl is reduced to propyl or *iso*propyl.

until 30 c.c. had been collected; it was then protected from moisture and refluxed for 12 hours. The isolated base (0·4 g., m. p. 218—220°) was crystallised from alcohol; it then had m. p. 224—225° and m. p. 226—227° when mixed with pure *neo*strychnine, m. p. 227°. The characteristic coupling with *p*-nitrobenzenediazonium chloride was noted.

*neo*Strychnine, m. p. 226—227°, had $[\alpha]_D^{18°}$ + 215° (*c*, 1·2 in chloroform) and $[\alpha]_D^{18°}$ + 90° (*c*, 1·2 in acetic acid).

Action of Raney Nickel on Pseudostrychnine Methyl Ether.—The ether (3·3 g.), Raney nickel sediment (3·5 c.c.), and xylene (120 c.c.) were employed and the process carried out as with the dihydro-derivative. The isolated base (2·5 g., m. p. 125° with frothing) was readily soluble in most organic solvents and crystallised from aqueous alcohol in slender needles, m. p. 130° with frothing (Found: C, 67·6; H, 6·7; OMe, 0·0; NMe, a trace. Found in material dried at 100° in a high vacuum: C, 72·4; H, 6·3. $C_{22}H_{24}O_3N_2,1{\cdot}5H_2O$ requires C, 67·3; H, 6·9. $C_{22}H_{24}O_3N_2$ requires C, 72·5; H, 6·6. $C_{21}H_{22}O_3N_2,1{\cdot}5H_2O$ requires C, 66·8; H, 6·7. $C_{21}H_{22}O_3N_2$ requires C, 72·0; H, 6·3%).

This product was obtained after dissolution in dilute hydrochloric acid and basification with ammonia. When, however, the xylene solution and chloroform washings were evaporated under reduced pressure, the residue could be crystallised from light petroleum (b. p. 100—120°) in anhydrous form, m. p. 116° (Found: C, 72·3; H, 6·8; OMe, 0·0%). Both specimens gave a yellow precipitate on coupling with *p*-nitrobenzenediazonium chloride. The form first described (0·2 g.) in 2N-hydrochloric acid (5 c.c.) was treated with a diazo-solution from *p*-nitroaniline (0·3 g.). After 10 minutes the solid was collected and crystallised several times from aqueous alcohol. It separated as light yellow needles, m. p. 240° (decomp.) (Found: C, 63·4; H, 5·8. $C_{26}H_{29}O_5N_5$ requires C, 63·3; H, 5·5. $C_{27}H_{27}O_6N_5$ requires C, 62·7; H, 5·3%). The substance gives the usual red coloration in alcoholic alkali. Neither this *x-hydroxyneostrychnine* (?) nor its dihydro-derivative (below) showed any signs of reaction with methanol.

x-Hydroxydihydrostrychnine (?).—(A) The above *x*-hydroxy*neo*strychnine (0·5 g.) in water (13 c.c.), N-hydrochloric acid (1·5 c.c.), and N-acetic acid (1·5 c.c.) was hydrogenated at the ordinary temperature and pressure in presence of platinic oxide (0·05 g.). In 1½ hours, 41 c.c. of hydrogen were absorbed (calc. for 2H, 43 c.c.). The isolated *base* (0·5 g., m. p. 112° with frothing) crystallised from aqueous alcohol in long, white needles, m. p. 114° (frothing) (Found: C, 66·8; H, 7·5. $C_{22}H_{26}O_3N_2,1{\cdot}5H_2O$ requires C, 67·1; H, 7·4. $C_{21}H_{24}O_3N_2,1{\cdot}5H_2O$ requires C, 66·5; H, 7·2%).

(B) The same base was obtained by hydrogenation at 60° in the presence of palladised charcoal.

(C) *x*-Hydroxy*neo*strychnine (0·05 g.) in warm 2N-hydrochloric acid (2·5 c.c.) was reduced by the addition of zinc dust (0·2 g.) during 15 minutes followed by heating on the steam-bath for ½ hour. A faint pink coloration indicated the formation of a small quantity of a strychnidine-type base. After filtration, precipitation with ammonia, and crystallisation from aqueous alcohol, needles, m. p. 114° with frothing, were obtained. The m. p. was the same on admixture with the analysed specimen.

x-Hydroxydihydrostrychnine does not react with *p*-nitrobenzenediazonium chloride in acid solution. When treated with Raney nickel in boiling xylene (9 hours) under the usual conditions, it was converted into *neo*strychnine, white prisms from alcohol, m. p. 222° and m. p. 224° on admixture with an authentic specimen, m. p. 224°. The characteristic reaction with *p*-nitrobenzenediazonium chloride was observed.

Reduction of neo*Strychnine.*—Zinc dust (1·0 g.) was gradually added during 10 minutes to a hot solution of *neo*strychnine (0·5 g., m. p. 224°) in 2N-hydrochloric acid (25 c.c.) and the mixture then heated for 1 hour on the steam-bath. The isolated base (0·5 g., m. p. 213°) crystallised from aqueous methanol in long, white needles, m. p. 217—218°, and 218° on admixture with dihydrostrychnine, m. p. 219°. The product gave no precipitate when *p*-nitrobenzenediazonium chloride was added to its acid solution. The formation of strychnine by reduction of pseudostrychnine under similar conditions shows that the double bond of the base cannot be reduced in this way, although some strychnidine is always produced. Using amalgamated zinc dust and dilute hydrochloric acid it was possible to isolate strychnidine from the products of the reaction.

Similarly the reduction of *neo*strychnine with amalgamated zinc dust and 4N-hydrochloric acid afforded dihydrostrychnidine-A, mixed with dihydrostrychnine. If the process can be improved so as to make it complete, details will be submitted; it is not yet a satisfactory method of preparation.

Derivatives of Pseudostrychnine and neo*Strychnine containing Phosphorus.*—(A) *Anhydropseudostrychninephosphorous acid.* A mixture of pseudostrychnine (5 g.), phosphorus trichloride (5 c.c.), and chloroform (50 c.c.) was refluxed for an hour. Next day the solution was evaporated under diminished pressure (steam-bath) and excess of dilute ammonia added to the residue. Acidification of the filtered solution with hydrochloric acid gave the crude product (4·0 g.). It crystallised from water, in which the substance is sparingly soluble, in white prisms containing phosphorus but free from chlorine. On being heated the substance darkens at 280°, shrinks at 295°, and decomposes vigorously at 315° (Found in material dried at 100°/15 mm.: C, 60·5; H, 5·9; N, 6·8. $C_{21}H_{23}O_5N_2P$ requires C, 60·9; H, 5·6; N, 6·8%). The *acid* exhibits a strong Otto reaction (violet) and dissolves in aqueous sodium hydrogen carbonate with effervescence. It remained unchanged after refluxing with dilute hydrochloric acid or aqueous sodium hydroxide. When sodium iodide was added before precipitation with hydrochloric acid the same product was obtained, but if perchloric acid was used to acidify the ammoniacal solution an abnormal *perchlorate* resulted. The sparingly soluble derivative crystallised from water in colourless needles, m. p. 266° (decomp.), $[\alpha]_D^{13°}$ − 21° (*c*, 2·0 in 2N-ammonia) (Found in material dried at 100° in a high vacuum: C, 53·1; H, 5·6; N, 6·3; Cl, 3·9. $2C_{21}H_{23}O_5N_2P,HClO_4,H_2O$ requires C, 53·3; H, 5·2; N, 5·9; Cl, 3·7%). A similar substance was obtained from dihydropseudostrychnine when it was treated in like manner and the ammoniacal solution acidified with 2N-perchloric acid. The white solid *perchlorate* crystallised from water in microscopic needles which darken from 230°, shrink at 330°, and decompose vigorously at 350° (copper block) (Found in material dried at 100°/15 mm.: C, 54·2; H, 5·8. $2C_{21}H_{23}O_5N_2P,HClO_4$ requires C, 54·0; H, 5·5%). Owing to its unexpected solubility in water, the free acid could not be isolated in this instance and acidification of the ammoniacal solution with hydrochloric acid gave no precipitate.

The interaction of pseudostrychnine with phosphoryl chloride or phosphorus pentachloride did not give rise to isolable compounds.

(B) *Tetrahydroanhydropseudostrychninephosphorous acid.* Anhydropseudostrychninephosphorous acid (0·2 g.) suspended in water (20 c.c.) at 60° was hydrogenated in the presence of platinic oxide (0·03 g.); 26 c.c. (1·93 mol.) of hydrogen were absorbed in 1 hour. The *acid*, obtained on concentrating the filtered solution, crystallised from water in small, white prisms, m. p. 302° (decomp.), $[\alpha]_D^{21°}$ + 67° (*c*, 1·2 in water) (Found in material dried at 100° in a high vacuum: C, 59·5; H, 7·0. $C_{21}H_{27}O_5N_2P,0{\cdot}5H_2O$ requires C, 59·1; H, 6·6%).

(C) *Bisanhydroneostrychninephosphoric acid.* A mixture of *neo*strychnine (2·0 g.) and syrupy phosphoric acid (8 c.c.; *d* 1·75) was treated for ½ hour at 150—160°. Water (15 c.c.) was added to the cooled solution and, after it had been kept in the refrigerator for 2 days, colourless crystals (1·0 g.) separated. The *acid* was readily soluble in dilute ammonia and crystallised from a small volume of water in prisms, m. p. 185° (decomp.) (Found in material dried at 100° in a high vacuum: C, 60·5; H, 5·8; N, 7·1. $C_{21}H_{23}O_5N_2P$ requires C, 60·8; H, 5·6; N, 6·8%). The strong Otto reaction was a purple coloration.

The hydrated *dihydro*-derivative, obtained as above by catalytic reduction (PtO_2) at 60° (volume of hydrogen absorbed equivalent to 2H), was readily soluble in water. It crystallised from methanol in short, colourless prisms which shrank at 307—312° and decomposed at 318—320° (Found in material dried at 100° in a high vacuum: C, 58·5; H, 6·1. $C_{21}H_{27}O_6N_2P$ requires C, 58·1; H, 6·3%).

(D) *Anhydroneostrychninephosphorous acid.* A mixture of *neo*strychnine (2·0 g.) and phosphorous acid (8 c.c. of molten acid of 100%) was heated for ½ hour at 150—160°. After addition of water (15 c.c.), white crystals (0·7 g.) gradually separated. The *acid* (soluble in ammonia) crystallised from a little water in prisms which shrank at 295° and decomposed at 316° (Found in material dried at 100°/15 mm.: C, 58·5; H, 6·1. $C_{21}H_{27}O_6N_2P$ requires C, 58·1; H, 6·3%). The usual Otto reaction was exhibited.

The *dihydro*-derivative prepared in the usual way (absorption, 1·1 mol.) was very easily soluble in water. It crystallised from methanol as stout needles which shrank at 295° and decomposed from 312°, $[\alpha]_D^{21°}$ + 67° (*c*, 1·2 in water) (Found in material dried at 100°/15 mm.: C, 61·6; H, 6·4. $C_{21}H_{25}O_6N_2P,0{\cdot}5H_2O$ requires C, 61·6; H, 6·5%).

(E) *Colour tests for the carbonyl group.* The compound (3 mg.) was heated at 100° with pyridine (1 c.c.) and *p*-nitrophenylhydrazine (0·5 mg.) for 30 minutes. Alcohol (4 c.c.) and then a few drops of 2N-sodium hydroxide were added.

All oxo-derivatives of strychnine and strychninonic acid gave red colorations; a negative reaction was light brown.

Pseudostrychnine and the anhydro-phosphorous and -phosphoric acids from *neo*strychnine gave positive indications for the carbonyl group. All the hydrogenated compounds and, curiously, anhydropseudostrychninephosphorous acid gave the same result as a blank.

Ozonisation of neo*Strychnine.*—*neo*Strychnine was recovered unchanged after attempted oxidation with atmospheric oxygen in the presence of Fehling's solution. The inactivity of dihydrostrychnine under these conditions has been reported by Prelog and Kočov (*Helv. Chim. Acta*, 1947, **30**, 369), and we have had the same experience.

Ozone (*ca.* 2 mols.) was passed during 1½ hours through a solution of *neo*strychnine (3·3 g.) in chloroform (30 c.c.) cooled in an ice-bath. After addition of water (50 c.c.) the mixture was refluxed for an hour, the chloroform was separated, extracted with dilute sulphuric acid, washed with aqueous ammonia and water, and dried. The oil obtained on removal of the solvent crystallised in contact with methanol (crude, m. p. 225—226°). After recrystallisation from the same solvent it had m. p. 236—237° (lit., 234—235°), and a mixture with an authentic specimen of Kotake's ketone (*loc. cit.*) had m. p. 235—236°. The *p*-nitrophenylhydrazone had m. p. 267—268°, alone or mixed with an authentic specimen (lit., 269—270°).

neo*Strychnine–Acetic Anhydride.*—A mixture of *neo*strychnine (3 g.) and acetic anhydride (30 c.c.) was heated for 20 hours at 100° and the excess of reagent removed from the brown solution by distillation at a low pressure. A solution of the residue in chloroform was repeatedly washed with dilute sulphuric acid (1·8 g. of unchanged bases were recovered on basification). The light brown solid left on removal of the chloroform was readily soluble in solvents, except light petroleum. Its benzene solution was passed through an alumina column, and a white solid was eventually obtained by fractional precipitation with light petroleum (b. p. 80—100°). In this condition it had m. p. 190° with frothing (Found: C, 68·7; H, 6·2. $C_{25}H_{28}O_5N_2$ requires C, 68·8, H, 6·5%). The investigation is incomplete; the *substance* does not afford a base on attempted hydrolysis with boiling dilute sulphuric acid.

Dibenzylidenestrychninonic Acid Hydrate.—A mixture of strychninonic acid (0·4 g.), benzaldehyde (0·3 g.), and alcohol (5 c.c.) was refluxed, and a solution of sodium (0·1 g.) in alcohol (5 c.c.) introduced; refluxing was continued for 15 minutes. The deep orange liquid was evaporated under diminished pressure, water added, and the filtered solution washed several times with ether. Acidification of the aqueous layer gave the *dibenzylidene* derivative as a light yellow solid which crystallised from aqueous dioxan in small, pale yellow needles, m. p. 181—183° (decomp.) (Found in material dried at 15° over phosphoric anhydride: C, 68·7; H, 5·7. Found in material dried at 100° in a high vacuum; C, 71·0; H, 5·4. $C_{35}H_{30}O_7N_2,H_2O$ requires C, 69·1; H, 5·3. $C_{35}H_{30}O_7N_2$ requires C, 71·2; H, 5·1%).

The corresponding *dianisylidene* derivative, prepared similarly, separated from aqueous alcohol as a light yellow solid, m. p. 203° (decomp.) (Found in material dried at 100° in a high vacuum: C, 68·1; H, 5·5. $C_{37}H_{34}O_9N_2$ requires C, 68·3; H, 5·3%).

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183. *Experiments on the Synthesis of Purine Nucleosides. Part XVII. The Preparation of 4-Glycofuranosidaminopyrimidines, and a Synthesis of 9-L-Arabofuranosido-2-methylthioadenine.**

By G. W. Kenner, B. Lythgoe, and A. R. Todd.

A description is given of model experiments on methods for preparing 4-glycofuranosidaminopyrimidines, necessary intermediates in the synthesis of natural purine nucleosides, by our general procedure. Successful methods devised were condensation of acetylated glycofuranoses with 4 : 6-diamino-2-methylthiopyrimidine, and condensation of acylated *aldehydo*-sugars with the same pyrimidine derivative to give Schiff's bases converted into glycosides on deacetylation. Thus *5-benzoyl* 2 : 3 : *4-triacetyl* aldehydo-L-*arabinose* was condensed with 4 : 6-diamino-2-methylthiopyrimidine and the acetyl groups removed from the product with methanolic ammonia. Subsequent debenzoylation, azo-coupling, and acetylation gave *6-amino-4-triacetyl-L-arabofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine* (VI; R = Ac). From (VI; R = Ac) 9-L-*arabofuranosido-2-methylthioadenine* has been synthesised.

In the course of model experiments it was observed that D-xylosyl-1-amine condenses readily with aniline to form aniline-D-xyloside.

The synthesis of 9-D-ribopyranosidoadenine (Baddiley, Kenner, Lythgoe, and Todd, Part X, *J.*, 1944, 657), a substance differing from natural adenosine only in the size of the lactol ring (Howard, Kenner, Lythgoe, and Todd, Part XV, *J.*, 1946, 861), was effected by the general method developed in this series for purine nucleoside synthesis. The initial step in this method is condensation of a suitable 4 : 6-diaminopyrimidine with an aldose in hot alcoholic solution in presence of an acidic catalyst, and it appears to yield invariably the corresponding 4-glycopyranosidamino-6-aminopyrimidine. In order to utilise the method for the natural nucleosides it was clear that some modification of the initial step to yield a furanoside rather than a pyranoside would be essential. The present paper records some of our model experiments directed to the solution of this problem; they include some novel methods of glycosidisation.

Although the products of condensation of 4 : 6-diaminopyrimidines with sugars in boiling alcoholic solution were pyranosides it seemed possible that condensation in the cold might yield furanosides by analogy with the synthesis of methylglucofuranoside by Fischer (*Ber.*, 1914, **47**, 1980) and the condensation of aniline with D-ribose by Lee, Solmssen, and Berger (U.S.P., 1945, 2,384,102). However, no reaction between diaminopyrimidines and sugars could be observed in the cold. This result was not entirely unexpected, for condensation even in boiling alcohol is sluggish, and some consideration was given to the use of a more reactive sugar derivative. Glycosyl-1-amines, as evidenced by their very ready hydrolysis, tend to eliminate their 1-amino-group, and this tendency should cause them to react with other amines forming *N*-glycosides. A few experiments showed that D-xylosyl-1-amine (de Bruyn and van Leent, *Rec. Trav. chim.*, 1895, **14**, 144) and aniline react in the cold in aqueous alcoholic solution or in alcoholic solution containing hydrogen chloride, ammonia being liberated and a crystalline aniline-D-xyloside produced. This product was similar in both initial optical rotation and velocity of mutarotation to the aniline-D-xyloside prepared by condensation of aniline with aqueous D-xylose at 100° (Weygand, *Ber.*, 1939, **72**, 1663) and despite some discrepancy in m. p. the identity of the two materials was confirmed by their conversion into identical triacetyl derivatives. The formation of *N*-glycosides by this means does not appear to have been previously recorded and the method might be of value in certain cases. It was not further pursued by us, however, since we were unable to condense xylosimine with 4 : 6-diaminopyrimidine in the cold, and other methods described below were already giving promise of success.

An alternative approach to the problem lay in modifying the existing general synthetic route by condensing a 4 : 6-diaminopyrimidine with a 5-acyl pentofuranose instead of with

* *Note added June 22nd*, 1948.—Since this paper was written further investigation has revealed that the Schiff-base route to 4-pentofuranosidaminopyrimidines, depending upon preferential removal of 2-, 3-, and 4-acetyl groups with retention of a 5-benzoyl group, is unreliable in operation. In subsequent experiments using the method described it was found that the 9-arabinosido-2-methylthioadenine isolated has a periodate titre varying between 2 and 3 mols./mol. This unreliability is even more marked in the ribose series. Full details of these extended studies and of modifications in method will be published in future papers. Meanwhile, it is clear that the route here described normally yields mixtures of furanoside and pyranoside, so that the homogeneity of such intermediates as (VI) must remain open to question.

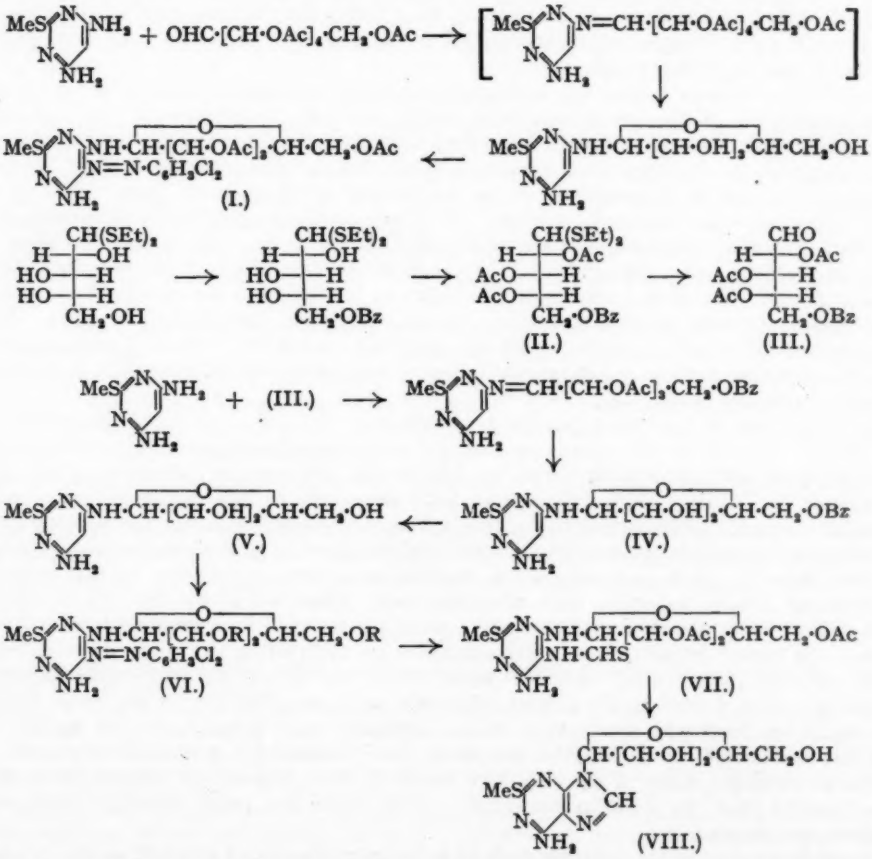
a free sugar. 5-Benzoyl D-ribofuranose was obtained as a syrup by benzoylating 2 : 3-*iso*propylidene methylribofuranoside (Levene and Stiller, *J. Biol. Chem.*, 1934, **104**, 301) and treating the product with dilute acid. Efforts to condense it with 4 : 6-diaminopyrimidine, 4 : 6-diamino-2-methylthiopyrimidine, or 4 : 6-diamino-5-thioformamidopyrimidine by heating in alcoholic solution in presence of acid catalysts by our standard procedure failed. Some reaction appeared to take place, however, since the boiling point of the benzene–alcohol distillates obtained during the experiments indicated that they contained water. The most likely explanation of these results seemed to be a preferential reaction of the furanose sugar component with the alcohol used as solvent. In an attempt to overcome this difficulty methyl cyanide was tried as a reaction medium, but no condensation occurred.

In view of the possibility that the above failures with 5-benzoyl ribose were due to the high reactivity of furanose sugars as compared with their pyranose isomers, the next step was clearly to reduce this reactivity by some means. It was shown that 2 : 3 : 4-triacetyl D-xylopyranose would not condense with 4 : 6-diamino-2-methylthiopyrimidine under the conditions employed successfully for D-xylose (Baddiley, Lythgoe, and Todd, Part III, *J.*, 1943, 571) and this suggested that acetylation of the free hydroxyl groups in a furanose might be a suitable method of deactivation for our purpose. As a model substance 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose (Compton and Wolfrom, *J. Amer. Chem. Soc.*, 1934, **56**, 1161) was selected. This substance was condensed with 4 : 6-diamino-2-methylthiopyrimidine in boiling alcoholic solution containing a trace of hydrogen chloride, water being removed azeotropically in the usual manner (Part III, *loc. cit.*). The crude product was directly coupled with diazotised 2 : 5-dichloroaniline in pyridine solution and the resulting mixture chromatographed on active alumina. The yellow amorphous product gave analytical results suggesting that it was a mixture of the expected 6-amino-4-tetra-acetyl-D-galactosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine with the corresponding sugar-free azo-compound in the proportion 3 : 1. An exactly similar product was obtained when the glycosidisation was repeated using boiling 2-ethoxyethanol as reaction medium; this condensation had to be stopped after only 90 minutes to avoid gross decomposition. Further purification of the products obtained in these reactions by chromatography on alumina was impossible, since it was shown in trial experiments that sugar-free azo-pyrimidines containing a 2-methylthio-substituent, and the corresponding acetylated azo-glycosides, are well-nigh inseparable on columns of this adsorbent. Unacetylated azo-glycosides on the other hand are very firmly adsorbed on alumina and cannot be eluted even with pyridine. Accordingly the crude mixture of azo-compounds obtained in the above condensations was deacetylated and then put on an alumina column which was washed with pyridine: the azo-glycoside then remained at the top of the column as a yellow band which could be extruded, and the glycoside acetylated on the adsorbent by treatment with acetic anhydride in pyridine solution. The product was eluted with ethyl acetate and purified by chromatography on alumina from the same solvent. In this way *6-amino-4-tetra-acetyl-D-galactofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine* was obtained as a deep yellow powder. Its formulation as a furanoside is supported by the fact that it is quite different from the corresponding *pyranoside* prepared by coupling *6-amino-4-D-galactopyranosidamino-2-methylthiopyrimidine* (prepared by Mr. H. Smith in this laboratory) with diazotised 2 : 5-dichloroaniline and acetylating the product in the normal manner. Application of this method for the production of furanosides to the synthesis of adenosine would, of course, involve the use of the hitherto unknown 2 : 3 : 5-triacetyl ribofuranose. The present inaccessibility of this compound, coupled with the parallel discovery of the following more attractive route to furanosidaminopyrimidines, led us temporarily to suspend exploitation of the method. It may be observed in passing that 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose did not condense under normal conditions with 4 : 6-diaminopyrimidine or with 4 : 6-diamino-5-thioformamidopyrimidine. It may be that other conditions might be found to effect condensation with the former compound, but this is known to be much less reactive than the 2-methylthio-compound in glycosidisations using free sugars.

Ring-chain tautomerism in *N*-glycosides has been the subject of much speculation and investigation since Schiff (*Annalen*, 1870, **154**, 30) first condensed aniline with D-glucose. On the evidence available up to the present it would appear that, although compounds possessing the open-chain Schiff's base structure may exist as transient intermediates in the mutarotation of *N*-glycosides, they have never been isolated, and all attempts to prepare them lead to the cyclic isomers. These facts suggested a novel method of glycoside synthesis which might prove applicable to the formation of furanosides or pyranosides at will, for it seemed reasonable to suppose that acylated *aldehydo*-sugars might condense with amines to form Schiff's

bases which, on removal of acyl groups, would be at once converted into the isomeric glycosides.

It was readily shown in preliminary experiments that benzaldehyde condenses with 4 : 6-diamino-2-methylthiopyrimidine in alcoholic solution although the Schiff's base was not isolated in crystalline form. When 2 : 3 : 4 : 5 : 6-penta-acetyl glucose was substituted for benzaldehyde condensation occurred at room temperature in alcoholic solution, more readily in presence of a little ammonium chloride. The Schiff's base was not isolated, the condensation product being at once deacetylated by means of sodium methoxide or methanolic ammonia. Attempts to crystallise the resulting glucoside failed and it was coupled in the usual manner with diazotised 2 : 5-dichloroaniline and the product acetylated giving 6-*amino*-4-*tetra-acetyl*-D-*glucopyranosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)-2-*methylthiopyrimidine* (I), identical with a specimen prepared in similar fashion from authentic crystalline 6-amino-4-D-glucopyranosidamino-2-methylthiopyrimidine (prepared by Mr. A. Holland in the course of other work in this laboratory). It is probable that the crude resinous glucoside obtained by deacetylating the Schiff's base is a mixture of α- and β-isomers, and in accordance with this view the acetylated azo-glucoside, isolated in a pure state, represented only part of the crude acetylated product. The production of a glucopyranoside by this method was expected but it contrasts with the production of *N*-acetyl-D-glucofuranosylamine by the action of ammonia on penta-acetyl *aldehydo*-D-glucose (Hockett and Chandler, *J. Amer. Chem. Soc.*, 1944, **66**, 957; Niemann and Hays, *ibid.*, 1945, **67**, 1302). It is interesting to note that the increased reactivity of 4 : 6-diamino-2-methylthiopyrimidine as compared with 4 : 6-diaminopyrimidine is again shown by the failure of the latter compound to condense with penta-acetyl *aldehydo*-glucose; 4 : 6-diamino-5-thioformamido-2-methylthiopyrimidine also fails to condense.



Adaptation of this new method of glycosidisation to the synthesis of furanosides by protecting the hydroxyl at C_5 in the sugar chain during the tautomeric change leading to the glycoside was

envisaged. The necessary differential acylation at C_5 in the *aldehydo*-sugar is simplest in the pentoses where the hydroxyl concerned is primary, and the benzoyl group seemed to fill the requirements of a protecting group, since it is readily removed by sodium methoxide but is stable to methanolic ammonia under conditions which cause complete removal of acetyl groups. For reasons of economy L-arabinose was chosen for our model experiments. *5-Benzoyl 2 : 3 : 4-triacetyl L-arabinose diethylthioacetal* (II), readily obtained from 5-benzoyl L-arabinose diethylthioacetal (Lieser and Schweizer, *Annalen*, 1935, **519**, 271), was converted by standard methods into *5-benzoyl 2 : 3 : 4-triacetyl* aldehydo-L-*arabinose* (III), a syrup which could not be crystallised. Condensation of (III) with 4 : 6-diamino-2-methylthiopyrimidine in alcoholic solution in presence of ammonium chloride gave a product which, largely freed from unreacted diamine by dissolution in chloroform, was deacetylated by treatment in the cold with methanolic ammonia. To avoid any complications arising from possible incomplete deacetylation or partial debenzoylation the product, presumably for the most part the glycoside (IV), was treated with hot sodium methoxide solution. As it was expected that the resulting product (V) would be very labile no attempt was made to remove unchanged diamine by alumina treatment, and the crude product was coupled directly with diazotised 2 : 5-dichloroaniline. The *azo-glycoside* (VI; R = H) was readily separated from sugar-free azo-diamine by chromatography on activated alumina, dry pyridine being used as solvent; the sugar-free compound passed rapidly through the column while the glycoside was firmly held and could subsequently be eluted by washing with pyridine to which sufficient water had been added to deactivate the alumina. The resinous product obtained was freed from other impurities by acetylation and subsequent chromatography; *6-amino-4-triacetyl-L-arabofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine* (VI; R = Ac) was thus obtained as a yellow powder; the pure *azo-glycoside* (VI; R = H) was obtained from the acetyl derivative by treatment with methanolic ammonia. As an alternative the crude azo-glycoside adsorbed on alumina could be acetylated *in situ* and eluted as the triacetyl derivative (VI; R = Ac); both methods gave comparable yields.

For purposes of comparison the pyranose compounds corresponding to (VI) were prepared. Condensation of 4 : 6-diamino-2-methylthiopyrimidine with L-arabinose in the ordinary way gave a syrup which was coupled with diazotised 2 : 5-dichloroaniline and the product acetylated. Chromatographic purification gave *6-amino-4-triacetyl-L-arabopyranosidamino-5-(2′ : 5′-dichlorobenzeneneazo)-2-methylthiopyrimidine* as yellow prisms quite distinct from (VI; R = Ac). Deacetylation gave the yellow *6-amino-4-L-arabopyranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine* which was not identical with (VI; R = H). There was thus good reason to believe that the azo-compounds (VI; R = H or Ac) were in fact furanosides. The only alternative, *viz.*, that they were α- or β-isomers of the pyranosides obtained by the direct glycosidisation process, seemed unlikely. Clearly, however, the simplest way to settle this point conclusively was by completion of the projected purine synthesis and application of the periodate oxidation method for determining lactol ring-structure (cf. Part XV, *loc. cit.*) to the synthetic purine glycoside.

The completion of a purine glycoside synthesis from (VI; R = H or Ac) presented certain new features. Hitherto the necessary 5-amino-group has been introduced into 6-amino-4-glycosidamino-2-methylthiopyrimidines by nitrosation followed by reduction (Part XI, *loc. cit.*; Part XVI, *J.*, 1947, 355); the use of azo-compounds as intermediates has so far been avoided in the case of derivatives containing a 2-methylthio-group. For the present synthesis we considered the nitrosation route but found that 6-amino-4-L-arabofuranosidamino-2-methylthiopyrimidine (V) gave a water-soluble nitroso-derivative, resembling in this respect the corresponding arabopyranoside and ribopyranoside (observation by Mr. H. T. Howard). Neither this product nor its acetyl derivative could be obtained in crystalline form. Attempts to obtain the acetyl deriative in a purer condition by acetylating (V) before nitrosation again yielded only a green syrup in poor yield. The use of nitroso-compounds as synthetic intermediates was therefore abandoned, although it is probable that a synthesis employing them might be developed by further work. Attention was instead devoted wholly to the use of the azo-compound (VI; R = Ac) as an intermediate for nucleoside synthesis. This involved an extended study of the reductive fission of the azo-group by various methods, since it was thought that the 2-methylthio-group would make the usual catalytic hydrogenation procedure troublesome.

A possible solution of the problem seemed to lie in treatment of (VI; R = Ac) in alcoholic solution with massive quantities of Raney nickel containing adsorbed hydrogen so as to cause simultaneous fission of the azo-group and removal of the 2-methylthio-group. When this

method was applied to 6-amino-4-triacetyl-D-xylopyranosido-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine in a model experiment, the expected 5 : 6-diamino-4-D-xylopyranosidaminopyrimidine was formed, although in rather low yield. An extended series of experiments showed, however, that high yields were unobtainable and the results were very variable; no method of controlling the reaction could be devised. The method proved equally unsatisfactory when applied to (VI; R = Ac). The indifferent results were doubtless due, in part, to formation of nickel complexes and the ready oxidation of the products, but the unusual reduction method, which probably does not cause simple fission of the azo-linkage in the manner of a normal hydrogenation, was almost certainly a contributory factor.

The important question of the mechanism of hydrogenolysis by Raney nickel under the conditions used in the normal desulphurisation method (Mozingo, *J. Amer. Chem. Soc.*, 1943, **65**, 1013) is not here directly relevant, and detailed consideration of it is deferred. Various observations suggest that it involves attack by atomic hydrogen with intermediate formation of free radicals; for example, Mozingo, Spencer, and Folkers (*J. Amer. Chem. Soc.*, 1944, **66**, 1859) record production of 43% of *N*-ethylaniline from hydrazobenzene under these conditions.

The unsatisfactory results obtained in these experiments led us to examine the application of normal catalytic hydrogenation procedures to 5-arylazopyrimidines containing a 2-methylthio-substituent. Using hydrogen at atmospheric pressure, a Raney nickel catalyst, although effective, had to be used in such large quantities that it was impracticable. The sulphur-resistant palladium–polyvinyl acetate catalyst of Kavanagh and Nord (*J. Amer. Chem. Soc.*, 1943, **65**, 2121) also brought about reduction of the azo-compound, but the low maximum concentration of catalyst made its use inconvenient. However, using only moderate quantities of Raney nickel, hydrogenation at 80° under 100 atmospheres' pressure was shown to be effective in model experiments. Simultaneously an independent approach was made using chemical methods of reduction, and zinc dust in weakly acid media was found to be effective.

Application of the zinc dust or catalytic methods of reduction to (VI; R = Ac), followed by treatment of the crude reduction product with dithioformic acid, gave 6-amino-5-thioformamido-4-triacetyl-L-arabofuranosidamino-2-methylthiopyrimidine (VII) as a colourless resin. Cyclisation of (VII) proceeded normally by boiling in alcoholic solution with sodium alkoxide, giving 9-L-*arabofuranosido-2-methylthioadenine* (VIII). The location of the sugar residue in (VIII) follows from its mode of preparation and is borne out by its insolubility in alkali, and the similarity between its absorption spectrum and that of 9-D-xylopyranosido-2-methylthioadenine. Its furanoside structure was rigidly established by periodate titration (Part VIII, *J.*, 1944, 592), 2 mols. of oxidant being consumed without production of formic acid; under similar conditions 2-methylthioadenine consumes 1 mol. of periodate (Part XI, *loc. cit.*).

The evidence presented defines the structure of the 9-L-arabofuranosido-2-methylthioadenine in all respects save for the configuration at the glycosidic carbon atom. In the absence of suitable data for comparison, the optical rotations of the glycoside and its periodate fission product do not provide reliable evidence on this point. The β-configuration might, however, be expected on general grounds since mutarotation to the β-form is normally found after reduction of 5-arylazopyrimidine intermediates (Part XIV, *J.*, 1946, 855).

The synthetic method described should be capable of extension to other 9-glycofuranosido-2-methylthioadenines and, since it has already been shown that 9-glycopyranosido-2-methylthioadenines can be converted into 9-glycopyranosidoadenines by desulphurisation with Raney nickel (Parts XI and XVI, *locc. cit.*), the results so far obtained indicate a route to the synthesis of adenosine itself. Experiments designed to effect such a synthesis are in progress.

Experimental.

Activated alumina used throughout was prepared by heating alumina hydrate (British Aluminium Co., Ltd.) to 360° during 5 hours.

Reaction of D-*Xylosyl-1-amine with Aniline.*—(1) Aniline (2·5 g.) and D-xylosyl-1-amine (4·05 g.) (De Bruyn and Van Leent, *loc. cit.*) were dissolved in water (20 c.c.) and alcohol (7 c.c.) and left for 12 days. Extraction with ether (3 portions of 150 c.c.) followed by evaporation of the ether yielded a syrup which solidified and crystallised from alcohol in fine needles (0·37 g.), m. p. 131° (Found in material dried at 56°: C, 58·6; H, 6·9; N, 6·2. Calc. for $C_{11}H_{15}O_4N$: C, 58·7; H, 6·7; N, 6·2%).

(2) Aniline (1·85 g.) and D-xylosyl-1-amine (3·0 g.) were shaken for 10 days with dry methanol (50 c.c.) and ethanolic hydrochloric acid (5 c.c. of N). The product, recrystallised from alcohol (0·82 g.), had m. p. 131°, undepressed by material prepared as in (1) above.

The glycoside was hydrolysed by refluxing for 30 minutes with N/10-sulphuric acid yielding aniline, identified as tribromoaniline, and D-xylose, identified as tetra-acetyl β-D-xylose.

Aniline-D-xyloside, prepared according to Weygand (*loc. cit.*), had m. p. 140°; a mixed m. p. with the

xyloside (m. p. 131°) described above was 133—135°. The crystalline form of the two specimens was identical, as was their mutarotation behaviour when examined in aqueous solution (*c*, 2·5 at 18°):

Time (mins.)	3	4	5	7	10	15	20	25	30
$[\alpha]_D$, xyloside, m. p. 131°	−66·4°	−63·6°	−61·5°	−60·6°	−56·5°	−56·2°	−55·1°	−55·1°	−54·9°
$[\alpha]_D$, xyloside, m. p. 140°	−67·2°	−66·2°	−65·2°	−63·3°	−61·0°	−59·6°	−58·4°	−58·4°	−58·0°

On acetylation with acetic anhydride in pyridine solution in the cold, both samples of xyloside gave the same product, m. p. and mixed m. p. 148—149°.

5-Benzoyl 2 : 3-iso*Propylidene Methyl-*D*-ribofuranoside.*—2 : 3-*iso*Propylidene methyl-D-ribofuranoside (19·2 g. : 0·01 mol.) (Levene and Stiller, *loc. cit.*), dissolved in pyridine (25 c.c.), was slowly treated with a solution of benzoyl chloride (15·15 g.; 0·011 mol.) in chloroform (25 c.c.) with shaking, the temperature being kept below 30°. After 2 days, solvent was evaporated, the residue treated with ice-water, and the mixture extracted several times with chloroform. The combined chloroform solutions were washed with ice-cold N-sulphuric acid, ice-cold aqueous sodium carbonate (10%), and ice-water (three times with each), and dried (Na_2SO_4). The syrup obtained on evaporation was distilled at 139°/2 × 10^{-3} mm. (yield, 22·2 g.; 75%) (Found in material redistilled at 170°/0·01 mm.: C, 63·1; H, 6·7. $C_{16}H_{20}O_6$ requires C, 62·4; H, 6·5%).

5-Benzoyl 1 : 2 : 3-*Triacetyl* D-*Ribose.*—5-Benzoyl 2 : 3-*iso*propylidene methyl-D-ribofuranoside (7·5 g.) was heated in boiling hydrochloric acid (100 c.c. of 0·04N) for 2½ hours. The syrup remaining after evaporation of the filtered solution, which had been shaken with barium carbonate, was extracted with warm *n*-butanol (70 c.c.). Thorough evaporation of the extract yielded a thick resin (5·7 g.; 92%); this was used in subsequent experiments as 5-benzoyl ribose. For identification the product (0·57 g.) was dissolved in pyridine (5 c.c.) and acetic anhydride (2·5 c.c.) and left overnight. Alcohol (3 c.c.) was added, and after 2 hours the liquid was evaporated, the residue dissolved in hot alcohol (5 c.c.), and the *5-benzoyl* 1 : 2 : 3-*triacetyl* D-*ribose*, which crystallised on cooling, collected and recrystallised from alcohol; colourless plates (0·22 g.), m. p. 117—118° (Found: C, 56·8; H, 5·5. $C_{18}H_{20}O_9$ requires C, 56·8; H, 5·3%).

*6-Amino-4-tetra-acetyl-*D*-galactofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.*—Tetra-acetyl-D-galactofuranose (0·7 g.) (Compton and Wolfrom, *loc. cit.*) and 4 : 6-diamino-2-methylthiopyrimidine (0·94 g.) were dissolved in boiling alcohol (25 c.c.), to which an alcoholic solution of hydrogen chloride (0·2 c.c. of 1·9N) had been added. Water was removed as the benzene–alcohol azeotrope through a 20 cm. Fenske column with reflux ratio head, and heating continued for 25 hours during 4 days. The resulting solution was then subjected to one of the following treatments.

(*a*) Solvent was evaporated and the residue extracted with chloroform. After evaporation of the chloroform extract the residue was dissolved in pyridine (10 c.c.) and treated with a neutral diazotised aqueous solution of 2 : 5-dichloroaniline (0·73 g.). Next day, after dilution with water (100 c.c.), the solid was collected, dried in a vacuum, and extracted with hot benzene (40 c.c.). The extract was adsorbed on alumina (40 g.) and the column (35 × 3 cm.) developed with ethyl acetate. The main broad yellow band was washed through rapidly and yielded a yellow solid (0·29 g.). This was evidently a mixture and could not be separated into its components by fractional crystallisation from benzene–alcohol (Found in material dried at 60°: C, 44·2; H, 3·9; N, 16·0. Calc. for a mixture containing 76% of $C_{23}H_{28}O_9N_6Cl_2S$ and 24% of $C_{11}H_{10}N_6Cl_2S$: C, 44·2; H, 3·9; N, 15·8%).

(*b*) A solution of sodium (0·023 g.) in alcohol (5 c.c.) was added and the solution boiled for 30 minutes before being poured into a neutral diazotised solution of 2 : 5-dichloroaniline (0·97 g.). After 15 minutes the precipitated solid was filtered off, washed with water, and dried at 50° (2·55 g.). It was dissolved in pyridine (25 c.c.) and adsorbed on alumina (50 g.) Washing the column with pyridine eluted a yellow band containing 4 : 6-diamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine (1·08 g.). The top portion of the column was removed, diluted with a little pyridine, and left overnight with acetic anhydride (10 c.c.). Alcohol (10 c.c.) was then added and the mixture kept for 1 hour in a bath of cold water. The solution was decanted and the alumina extracted with cold ethyl acetate–pyridine (9 : 1.; 200 c.c. in 6 portions). The solution and extracts were evaporated, taken up in ethyl acetate (15 c.c.) and chromatographed on alumina (50 g.; column 25 × 2 cm.). The broad yellow band which was first eluted contained an amorphous material which separated from alcohol as a yellow powder of indefinite m. p. *ca.* 140°; $[\alpha]_D^{20°}$ − 335° (± 20°) (*c*, 0·17 in chloroform) (Found in material dried at 80°: C, 45·3; H, 4·3; N, 12·8. $C_{23}H_{28}O_9N_6Cl_2S$ requires C, 45·5; H, 4·2; N, 12·7%).

*6-Amino-4-*D*-galactopyranosidamino-2-methylthiopyrimidine* (by Mr. H. Smith).—Ammonium chloride (1 g.), D-galactose (8 g.), and 4 : 6-diamino-2-methylthiopyrimidine (24 g.) were refluxed in absolute alcohol (300 c.c.) for 8 hours in a flask fitted with a Fenske column with reflux ratio head, water being removed azeotropically with benzene. Next day the mixture, which contained a small amount of crystalline material, was adsorbed on active alumina (1 kg.) which was washed with alcohol to remove unreacted diamine. Elution with water (2·5 l.) and concentration to small bulk caused crystallisation of the *galactoside* in pellet-like aggregates of colourless hydrated needles (10·15 g.; 72%). On being heated, the recrystallised product appeared to lose water at 95—96° and had m. p. *ca.* 176° (decomp.); $[\alpha]_D^{20°}$ − 58° (± 0·6°) (*c*, 0·3507 in water) (Found in material dried at 100°/0·1 mm.: C, 40·8; H, 5·7; N, 17·6. $C_{11}H_{18}O_5N_4S$ requires C, 41·4; H, 5·7; N, 17·6%).

*6-Amino-4-tetra-acetyl-*D*-galactopyranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.*—6-Amino-4-D-galactopyranosidamino-2-methylthiopyrimidine (0·5 g.) was suspended in water (5 c.c.) and treated with a diazotised solution of 2 : 5-dichloroaniline (0·4 g.), followed immediately by excess of aqueous sodium bicarbonte. After 1 hour the precipitated solid was filtered off, washed with water, and dried at 60° (0·62 g.). It was kept overnight in pyridine (10 c.c.) and acetic anhydride (3 c.c.); alcohol (5 c.c.) was then added, and after 1 hour the solvent was evaporated. The residue, dissolved in ethyl acetate, was chromatographed on a column of alumina (100 g.; 3 cm. bore). Evaporation of the eluate

of the broad yellow band yielded a resin (0·52 g.) which, on crystallisation from alcohol (10 c.c.) containing a little ethyl acetate, gave fine orange needles, m. p. 242—243°; $[\alpha]_D^{20°}$ − 443° (± 10°) (*c*, 0·26 in chloroform) (Found in material dried at 140°: C, 45·0; H, 4·5; N, 12·4. $C_{25}H_{28}O_9N_6Cl_2S$ requires C, 45·5; H, 4·2; N, 12·7%).

6-Amino-4-tetra-acetyl-D-glucopyranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—(a) *From penta-acetyl* aldehydo-D-*glucose*. Ammonium chloride (0·03 g.; 0·6 mol.) and 4 : 6-diamino-2-methylthiopyrimidine (1·26 g.; 8·0 mols.) were dissolved in boiling absolute alcohol (40 c.c.) and 2 : 3 : 4 : 5 : 6-penta-acetyl D-glucose (0·78 g.; 2·0 mols.) (Wolfrom, *J. Amer. Chem. Soc.*, 1929, **51**, 2188) added, the mixture being shaken until solution was complete. After 24 hours the solvent was evaporated and the residue left for two days with methanolic ammonia (30 c.c. of 5N). The residue obtained on evaporation was dissolved in alcohol (25 c.c.) and adsorbed on a column of alumina (30 g.; 3 cm. bore), which was washed with alcohol (70 c.c.) to remove unchanged diamine (1·06 g.; 6·8 mols.) and eluted with water (70 c.c.). No crystalline glucoside separated in 3 days from the eluate concentrated to 8 c.c. A neutral diazotised solution of 2 : 5-dichloroaniline (0·32 g.; 2 mols.) was added and the precipitated azo-compound collected after ½ hour and dried (0·48 g.; 51%). The crude material was acetylated by being kept overnight with pyridine (4 c.c.) and acetic anhydride (2 c.c.). The resinous product was chromatographed on alumina (40 g.; 2·5 cm. bore) in ethyl acetate; evaporation of the eluate from the broad yellow band yielded an orange resin (0·51 g.; 39%). After three recrystallisations from alcohol, the product formed needles, m. p. 218—219°; $[\alpha]_D^{20°}$ − 456° (± 40°) (*c*, 0·08 in chloroform) (Found in material dried at 100°: C, 45·8; H, 4·0; N, 12·5. $C_{25}H_{28}O_9N_6Cl_2S$ requires: C, 45·5; H, 4·2; N, 12·7%).

(b) *From 6-amino-4-D-glucopyranosidamino-2-methylthiopyrimidine.* The crystalline glucoside (0·64 g.; prepared by Mr. A. Holland) was mixed with a diazotised solution of 2 : 5-dichloroaniline (0·4 g.) and rapidly neutralised by addition of an aqueous solution of sodium bicarbonate (2 g.). After 1 hour the azo-compound was collected. Recrystallised from alcohol–pyridine it had m. p. 268°. A portion of the crude material (0·15 g.) was left overnight with pyridine (3 c.c.) and acetic anhydride (1 c.c.). Alcohol (2 c.c.) was then added, the solvent evaporated after 1 hour, and the residue recrystallised from benzene; fine yellow needles, m. p. 220—221°, undepressed in admixture with material prepared as in (a) above; $[\alpha]_D^{20°}$ − 486° (± 10°) (*c*, 0·25 in chloroform).

5-Benzoyl 2 : 3 : 4-Triacetyl L-Arabinose Diethylthioacetal.—Acetic anhydride (100 c.c.) was added slowly to an ice-cold stirred solution of 5-benzoyl L-arabinose diethylthioacetal (36 g.; Lieser and Schweizer, *Annalen*, 1935, **519**, 271) in dry pyridine (150 c.c.), and the mixture left overnight and then poured into ice-water (2 l.). Extraction with chloroform and evaporation of the dried extract gave a syrup which was dissolved in warm methanol. Water was added until the solution became slightly opalescent. The *triacetyl* compound slowly separated in colourless prisms (42 g.), m. p. 44—45°, unchanged on further recrystallisation; $[\alpha]_D^{14°}$ − 26·8° (*c*, 2·0 in chloroform) (Found: C, 54·8; H, 6·3. $C_{22}H_{30}O_9S_2$ requires C, 54·3; H, 6·2%).

5-Benzoyl 2 : 3 : 4-Triacetyl L-Arabinose.—Cadmium carbonate (30 g.) and 5-benzoyl 2 : 3 : 4-triacetyl L-arabinose diethylthioacetal (15·5 g.) were stirred with acetone (57·6 c.c.) and water (20 c.c.), and a solution of mercuric chloride (31·2 g.) in acetone (57·6 c.c.) slowly dropped in. After 15 hours' stirring at room temperature with occasional addition of fresh cadmium carbonate, the temperature was raised to 50° for 15 minutes, and to 70° for a further 15 minutes. The cooled mixture was filtered, and the residue well washed with acetone. The combined filtrate and washings were evaporated and the residue was repeatedly evaporated with dry acetone, extracted with chloroform (200 c.c.), and the extract dried (Na_2SO_4). Evaporation of the extract gave *5-benzoyl 2 : 3 : 4-triacetyl L-arabinose* as a clear syrup which gave a positive Schiff's test, but could not be crystallised. Distillation at 170° (bath temp.)/3 × 10^{-4} mm. gave a yellowish syrup (Found: C, 57·7; H, 5·5. $C_{18}H_{20}O_9$ requires C, 56·8; H, 5·3%).

6-Amino-4-triacetyl-L-arabofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—(1) Ammonium chloride (0·56 g.) and 4 : 6-diamino-2-methylthiopyrimidine (20·2 g.) were dissolved in boiling absolute alcohol (480 c.c.) and added to syrupy 5-benzoyl 2 : 3 : 4-triacetyl L-arabinose prepared from the mercaptal (15·5 g.), and the resulting solution was left for 20 hours. The solution was evaporated and the residue extracted with chloroform (160 c.c.), leaving unchanged diamine (13·8 g.). The chloroform extract was evaporated, the residue left for 2 days with methanolic ammonia (320 c.c. of 5N) to remove the acetyl groups, and the solution evaporated. A solution of sodium (1·47 g.) in methanol (200 c.c.) was added, and the whole boiled for 30 minutes, cooled, and concentrated to 80 c.c. After addition of glacial acetic acid (3·05 c.c.) the solution was poured into a neutral diazotised solution of 2 : 5-dichloroaniline (6·5 g.) and the precipitated yellow solid (15·5 g.) collected after 15 minutes, washed with water, and dried. The crude azo-compound was dissolved in pyridine (200 c.c.) and adsorbed on a column of alumina (500 g.; 8·5 cm. bore), which was then washed with pyridine to remove sugar-free azo-compound. The upper part of the column containing the adsorbed azo-glycoside was extruded, washed with water (80 c.c.), and eluted with pyridine–water (9 : 1; 1·2 l.). Evaporation of the eluate gave a resin which was left overnight with acetic anhydride (15 c.c.) and pyridine (30 c.c.). Excess of acetic anhydride was decomposed with alcohol, the solution evaporated, and the residue chromatographed on active alumina (180 g.; column 5·5 cm. bore) in ethyl acetate solution. The resinous acetylated *azo-glycoside* (5·85 g.; 31%) passed through as a pure yellow band. On dissolution in hot alcohol and allowing the solution to cool, the product was obtained as a yellow amorphous powder, m. p. *ca.* 135°; it had $[\alpha]_D^{20°}$ − 124° (± 10°) (*c*, 0·25 in chloroform) (Found in material dried at 100°: C, 45·3; H, 4·4; N, 13·9. $C_{23}H_{24}O_7N_6Cl_2S$ requires C, 45·0; H, 4·1; N, 14·3%).

(2) The crude azo-glycoside (1 g.) obtained as in (1) above was stirred with pyridine (25 c.c.) and adsorbed on an alumina column (30 × 3 cm.) which was well washed with pyridine. The upper half of the column was extruded and left overnight with acetic anhydride (10 c.c.) and pyridine (20 c.c.). Unchanged acetic anhydride was decomposed by alcohol (10 c.c.) and the product eluted with hot ethyl acetate. Purification by chromatography gave acetylated azo-glycoside (0·4 g.; 33%), identical with that obtained by (1).

6-Amino-4-L-arabofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—A solution of the above acetylated azo-glycoside (0·3 g.) in chloroform (8 c.c.) and saturated methanolic ammonia (20 c.c.) was left for 3 days then evaporated to dryness. Recrystallisation of the residue from alcohol yielded the *azo-glycoside* as yellow prisms, m. p. 217—218° (Found in material dried at 140° : C, 41·2; H, 4·1; N, 17·7. $C_{16}H_{18}O_4N_6Cl_2S$ requires C, 41·6; H, 3·9; N, 18·2%).

6-Amino-4-triacetyl-L-arabopyranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—Ammonium chloride (0·3 g.), L-arabinose (5 g.), and 4 : 6-diamino-2-methylthiopyrimidine (10 g.) were heated in boiling absolute alcohol (80 c.c.) for 1 hour. The flask was then fitted with a Fenske column with reflux ratio head and the solution refluxed for 8 hours, water being removed azeotropically with benzene. Next day the mixture was adsorbed on active alumina (500 g.) which was washed with alcohol (3·5 l.); evaporation of the washings gave unchanged diamine (5 g.). The glycoside was eluted with water (6 l.) and the eluate concentrated to 80 c.c. As no crystals separated, a portion (three-tenths = 0·01 mole of sugar) of this solution was treated with a neutral diazotised solution of 2 : 5-dichloroaniline (1·62 g.), and the yellow precipitate (3·3 g.) collected and dried. Acetylation of this by leaving it overnight with acetic anhydride (5 c.c.) in pyridine (15 c.c.) and purification of the product by chromatography in ethyl acetate solution gave the acetylated *azo-glycoside* (2·7 g.; 46%) as an orange yellow powder. Slow crystallisation from alcohol containing a little ethyl acetate gave the compound in orange prisms which sintered somewhat at 160° and melted at 213—214°; $[\alpha]_D^{20°}$ − 209° (± 5°) (*c*, 0·42 in chloroform) (Found in material dried at 100° : C, 44·7; H, 4·2; N, 14·3. $C_{22}H_{24}O_7N_6Cl_2S$ requires C, 45·0; H, 4·1; N, 14·3%).

6-Amino-4-L-arabopyranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—Sodium methoxide (from 0·05 g. of sodium in 3 c.c. of methanol) was added to the above triacetyl compound (0·5 g.) in chloroform (3 c.c.) and the mixture left overnight and worked up in the usual manner. The *azo-glycoside* crystallised from pyridine–alcohol in flat orange prisms, m. p. 233—234° (Found in material dried at 140° : N, 17·9. $C_{16}H_{18}O_4N_6Cl_2S$ requires N, 18·2%).

9-L-Arabofuranosido-2-methylthioadenine.—(1) Zinc dust (8 g.) and 6-amino-4-triacetyl-L-arabinofuranosidamino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine (1 g.) were stirred vigorously in boiling ethyl acetate (80 c.c.), and acetic acid (4 c.c.) in ethyl acetate (40 c.c.) added dropwise during 1 hour. The liquid was then decanted, the zinc extracted with warm ethyl acetate (2 × 50 c.c.), and the combined solution and extracts were evaporated to dryness in a nitrogen atmosphere and the resin triturated with *n*-hexane. The insoluble residue was dissolved in ethyl acetate (60 c.c.), dithioformic acid (from 4 g. of sodium salt) added, and the mixture refluxed for 2 hours before the addition of a second portion of dithioformic acid (from 2 g. of sodium salt). Heating was continued for a further hour and the mixture set aside overnight. The solution was decanted, the residue extracted with boiling alcohol (4 × 50 c.c.), and the combined solution and extracts were evaporated to dryness. The residue was dissolved in ethyl acetate (25 c.c.) and chromatographed on a column of neutral alumina (35 g.; 3 cm. bore), the column being developed with ethyl acetate (80 c.c.) before elution with pyridine (100 c.c.); evaporation of the eluate gave a colourless resin (450 mg.) consisting mainly of the thioformamido-compound (IX) contaminated with some sugar-free material.

The dried crude thioformamido-compound (450 mg.) was heated under reflux with sodium methoxide (53 mg.) and absolute alcohol (20 c.c.) in a nitrogen atmosphere for 4 hours. The solution was evaporated, water (6 c.c.) was added, and the mixture set aside for 2 days at 0°. The *9-L-arabofuranosido-2-methylthioadenine* which separated (138 mg.; 26% of theory calculated on acetylated azo-glycoside) was collected and recrystallised from hot water; it then formed colourless needles, m. p. 274° (decomp.); $[\alpha]_D^{18°}$ + 46° (± 10°) (*c*, 0·13 in water) (Found in material dried at 140° : C, 42·3; H, 4·9; N, 22·8. $C_{11}H_{16}O_4N_5S$ requires C, 42·2; H, 4·8; N, 22·4%). Ultra-violet absorption : In N/20-hydrochloric acid, maxima at 2200 A. (ε, 15,900) and 2680 A. (ε, 16,300). In N/20-sodium hydroxide, maxima at 2340 A. (ε, 21,400) and 2755 A. (ε, 15,500).

Periodate titration. 46·7 Mg. of glycoside in water + 5 c.c. of sodium metaperiodate (0·238M) made up to 25 c.c. total volume. Periodate consumed ≡ 2·1 mols.; liberation of acid, nil. Rotation of solution after oxidation, + 0·03° (± 0·02°) (*l*, 1 dm.), i.e. $[M]_D^{18°}$ of fission product, + 5000° (± 3000°).

Note. As the presence of sugar-free material in the crude thioformamido-compound causes wastage of reagent it was found desirable in later runs to employ twice the amount of sodium methoxide used in the above preparation.

(2) The acetylated azo-furanoside (1 g.) and Raney nickel (0·2 g.) were stirred with ethyl acetate (100 c.c.) and hydrogen under 90 atmospheres at 80° for 8 hours. The liquid was decanted, the nickel washed with cold alcohol, and the solution filtered with supercel; subsequent operations were as in (1) above. Yield of crude thioformamido-compound, 325 mg. Yield of 9-L-arabofuranosido-2-methylthioadenine, 61 mg.

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184. *Experiments on the Synthesis of Purine Nucleosides. Part XVIII. A Synthesis of* 9-D-*Glucopyranosidoadenine.*

By A. Holland, B. Lythgoe, and A. R. Todd.

9-D-Glucopyranosidoadenine has been synthesised by two methods each using the unambiguous general route to 9-glycosidopurines described in earlier papers of this series. In the first of these, starting from 4 : 6-diamino-2-methylthiopyrimidine and D-glucose, 9-D-*glucopyranosido-2-methylthioadenine* was prepared and the methylthio-group removed by treatment with Raney nickel. In the second a more direct synthesis was employed starting from 4 : 6-diaminopyrimidine. The yields in both syntheses were low, but the 9-D-glucopyranosidoadenine, isolated as its picrate, was identical with the adenine glucoside of Fischer and Helferich (*Ber.*, 1914, **47**, 210). This provides additional chemical proof that the sugar residue in adenosine is located at N_9 in the purine skeleton.

In Part XVI (*J.*, 1947, 355) we described the synthesis of 9-β-D-mannopyranosidoadenine, using a method developed in earlier papers which established beyond doubt the position of the sugar residue in the product. One of our objects in preparing this mannoside was to demonstrate directly that in adenosine the ribofuranose residue is attached to N_9 of the purine skeleton, and this aim was accomplished by showing that identical dialdehydes arose from periodate oxidation of the synthetic mannopyranoside on the one hand and of the natural ribofuranoside on the other. The same result could have been achieved with equal validity in an alternative way, which it was our original intention to follow. We had already shown (Davoll, Lythgoe, and Todd, Part XII, *J.*, 1946, 833) that the two sugar residues are present in identical positions in adenosine and in Fischer and Helferich's adenine glucoside, a synthetic product which is obtained by interaction of acetobromoglucose with 2 : 8-dichloroadenine silver, followed by deacetylation and dehalogenation of the product (*Ber.*, 1914, **47**, 210; Davoll, Lythgoe, and Todd, *loc. cit.*). A chemical proof that Fischer and Helferich's compound is in fact a 9-glycoside would therefore establish the same structural feature for adenosine. Accordingly, we commenced the synthesis of 9-D-glucosidoadenine by an unambiguous route, but difficulties in securing satisfactory yields during the later stages caused delay, with the result that the synthesis of the corresponding mannosides, and the proof using the alternative method, were completed first. It seemed desirable in spite of the poor yields obtained to place on record the experiments relating to the synthesis of the glucoside, and a description of this work forms the subject of the present paper.

Condensation of 4 : 6-diamino-2-methylthiopyrimidine and D-glucose by the method described in Part III (*J.*, 1943, 571) gave a crystalline 6-*amino*-4-D-*glucosidamino*-2-*methylthiopyrimidine*, which was used in our first experiments as starting material for a synthesis of 9-D-glucosidoadenine by a route similar to that used for synthesis of 9-D-xylopyranosidoadenine (Part XI, *J.*, 1945, 556). Treatment with nitrous acid converted the 4-D-glucosidamino-compound into a 5-nitroso-derivative which was reduced and the resulting 5-amino-derivative converted without purification into 6-*amino*-5-*thioformamido*-4-D-*glucosidamino*-2-*methylthiopyrimidine*. The last was successfully cyclised by heating it with sodium methoxide in ethanol (Part XIII, *J.*, 1946, 852), giving 9-D-glucosido-2-methylthioadenine. This compound was difficult to isolate in satisfactory yield in pure condition, owing to its high solubility in water and apparently low crystallising power. The methylthio-group was replaced by hydrogen by refluxing an alcoholic solution of the resinous triacetyl derivative with nickel containing adsorbed hydrogen, the acetyl groups then being removed by treatment with methanolic ammonia. The resulting 9-D-glucosidoadenine could not be obtained crystalline, owing to unfavourable solubility and the small amounts available, but treatment with picric acid gave a picrate identical in properties with the picrate of adenine glucoside prepared by Fischer and Helferich's method.

The low yields in the above synthesis made it desirable to explore the alternative and more direct method of synthesis starting from 6-*amino*-4-D-*glucosidaminopyrimidine*. This was obtained in satisfactory yield by condensation of the components in ethanol containing hydrogen chloride. It coupled readily with diazotised 2 : 5-dichloroaniline, giving 6-*amino*-5-(2′ : 5′-*dichlorobenzeneazo*)-4-D-*glucosidaminopyrimidine*, and the corresponding *tetra-acetyl* derivative was catalytically reduced to 5 : 6-*diamino*-4-*tetra-acetyl*-D-*glucosidaminopyrimidine*. Treatment with dithioformic acid in ethanol converted this into its 5-thioformyl derivative, but although purified chromatographically the product could not be obtained crystalline, and again the yield was rather poor. Cyclisation with sodium methoxide in ethanol gave a product from which, by

treatment with picric acid, 9-D-glucosidoadenine picrate was obtained, identical with material obtained by the first route.

These experiments demonstrate the nature of Fischer and Helferich's adenine glucoside as a 9-D-glucosidoadenine, and confirm the results of Part XVI (*loc. cit.*), demonstrating that adenosine is a 9-glycosido-adenine.

Experimental.

6-Amino-4-D-glucosidamino-2-methylthiopyrimidine.—4 : 6-Diamino-2-methylthiopyrimidine (22·5 g.), D-glucose (11·3 g.), and ammonium chloride (0·75 g.) were heated under reflux in dry ethanol (300 c.c.) for 12 hours, water generated in the reaction being removed periodically by addition of dry benzene and distillation of the azeotropic mixture through an efficient column. The cooled solution was filtered through activated aluminium oxide (1000 g.) which was washed first with ethanol (3·5 l.) to remove unchanged diamine, and then with water (5 l.). The aqueous eluate was evaporated under reduced pressure to small volume (100 c.c.) and kept overnight; the *glucoside* which had then separated was recrystallised from water. It formed colourless needles, softening at 145° but without definite m. p.; $[\alpha]_D^{20°}$ — 112° (*c*, 4·56 in water) (Found : C, 40·5; H, 6·0; N, 17·1. $C_{11}H_{18}O_5N_4S,\frac{1}{2}H_2O$ requires C, 40·4; H, 5·8; N, 17·1%) (yield, 10 g.).

Hydrolysis. A portion (0·3 g.) of the above glucoside was heated under reflux for 2 hours with 0·1N-sulphuric acid (21 c.c.), the solution neutralised with sodium hydroxide and evaporated to dryness, and the residue extracted with hot ethanol (30 c.c.). The extract was filtered through activated aluminium oxide (15 g.) which was washed with ethanol (45 c.c.), and filtrate and washings united and evaporated, giving 4 : 6-diamino-2-methylthiopyrimidine, characterised as the picrate, m. p. 212° (decomp.) alone or mixed with authentic material. A second portion of glucoside (0·12 g.) was hydrolysed for 2 hours with boiling N-hydrochloric acid (5 c.c.), and then worked up in a similar fashion. The aluminium oxide after being washed with ethanol was eluted with water, the aqueous eluate on treatment with phenylhydrazine hydrochloride and sodium acetate giving glucosazone.

Acetylation. 6-Amino-4-D-glucosidamino-2-methylthiopyrimidine (1 g.), acetic anhydride (4 c.c.), acetyl chloride (0·2 c.c.), and pyridine (15 c.c.) were heated on the steam-bath for 1 hour, the cooled solution treated with ethanol (20 c.c.), and, after 2 hours, solvents were removed under reduced pressure. Crystallisation of the residue from ethanol gave *6-acetamido-4-tetra-acetyl-D-glucosidamino-2-methylthiopyrimidine* (1 g.) as needles, m. p. 194°; $[\alpha]_D^{17°}$ — 33° (*c*, 1·13 in pyridine) (Found : C, 47·5; H, 5·5; N, 11·0. $C_{21}H_{29}O_{10}N_4S$ requires C, 47·7; H, 5·3; N, 10·6%).

6-Amino-5-thioformamido-4-D-glucosidamino-2-methylthiopyrimidine.—To a solution of 6-amino-4-D-glucosidamino-2-methylthiopyrimidine (5 g.) and sodium nitrite (1 g.) in water (150 c.c.), which was cooled to 5°, glacial acetic acid (2 c.c.) was added. After the mixture had been kept at 0° overnight the blue nitroso-compound was collected, washed with cold water, and suspended in ice-cold water (40 c.c.). To the well-cooled suspension ammonium sulphide solution (2·7 c.c. of aqueous ammonia, *d* 0·88, and 40 c.c. of water saturated with hydrogen sulphide at 0°) was added, and a vigorous current of hydrogen sulphide passed through the mixture for 1 hour, after which it was evaporated to dryness under reduced pressure and the residue extracted with hot water (170 c.c. at 90°). The extract, cooled to 40°, was treated with sodium dithioformate solution (4·6 g. hexahydrate in 20 c.c. water) and the solution kept overnight. The *thioformamido*-compound collected and recrystallised from water had m. p. 204—205° (Found : C, 36·3; H, 5·3; N, 17·8. $C_{12}H_{19}O_5N_5S_2,H_2O$ requires C, 36·4; H, 5·3; N, 17·7%) (yield, 2 g.).

Acetylation. Acetylated with pyridine and acetic anhydride in the usual way the above thioformamido-compound (6·5 g.) gave *6-amino-5-thioformamido-4-tetra-acetyl-D-glucosidamino-2-methylthiopyrimidine*, forming crystals from ethanol–chloroform, m. p. 218—219° (Found : C, 43·8; H, 4·9; N, 12·6. $C_{20}H_{27}O_9N_5S_2$ requires C, 44·0; H, 4·9; N, 12·8%) (Yield, 7 g.).

9-D-Glucopyranosido-2-methylthioadenine.—The acetyl-free thioformamido-compound (200 mg.) and sodium methoxide (30 mg.) were dissolved in dry ethanol (16 c.c.) and the solution heated under reflux in a slow stream of nitrogen for 5 hours, then kept at 0° for 2 hours and evaporated to dryness under reduced pressure. The residue was dissolved in cold water, N-sulphuric acid (0·7 c.c.) added, and the solution warmed with barium carbonate for a few minutes, filtered, and evaporated to dryness. Recrystallisation from ethanol gave the *glucoside* as a light brown powder, m. p. 173—176° (Found : C, 39·9; H, 5·7; N, 19·5. $C_{12}H_{17}O_5N_5S,H_2O$ requires C, 39·9; H, 5·3; N, 19·4%) (yield, 100 mg.).

6-Amino-4-D-glucosidaminopyrimidine.—4 : 6-Diaminopyrimidine (18 g.) and D-glucose (9 g.) were heated under reflux in dry ethanol (500 c.c.) containing hydrogen chloride (6 c.c. of ethanol saturated with dry hydrogen chloride at 0°) for 40 hours, with azeotropic removal of water. Filtration through activated aluminium oxide as usual, followed by washing with ethanol, elution with water, and evaporation of the aqueous eluate, gave *6-amino-4-D-glucosidaminopyrimidine* as colourless needle-clusters which on rapid heating melted at 191°, resolidified, and finally melted at 208—209° (Found : C, 41·8; H, 6·4; N, 19·3. $C_{10}H_{16}O_5N_4,H_2O$ requires C, 41·4; H, 6·2; N, 19·3%) (yield, 8 g.).

6-Amino-4-tetra-acetyl-D-glucosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine.—A suspension of the above glucoside (5·5 g.) in water (50 c.c.) was treated with a solution of 2 : 5-dichlorobenzenediazonium chloride, prepared in the usual way from 2 : 5-dichloroaniline (4 g.) in water (120 c.c.) containing concentrated hydrochloric acid (25 c.c.) and sodium nitrite (1·7 g.). The solution was then immediately neutralised with sodium hydrogen carbonate solution, and after standing overnight the red azo-compound was collected and dried (yield, 7·4 g.). This crude material was dissolved in pyridine (150 c.c.), treated with acetic anhydride (37·5 c.c.), and, after standing overnight, excess of acetic anhydride was decomposed with ethanol (60 c.c.) and solvents removed under reduced pressure. The residue was dissolved in ethyl acetate and filtered through a column of activated aluminium oxide from which washing with the same solvent removed the desired substance, which was then obtained by evaporation of the eluate and crystallisation of the residue from benzene. *6-Amino-4-tetra-acetyl-D-glucosidamino-5-*

(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine* separated as pellet-like needle aggregates, m. p. 236—237°; $[\alpha]_D^{18°}$ − 360° (*c*, 3·76 in chloroform) (Found: C, 45·8; H, 4·3; N, 13·7. $C_{23}H_{24}O_8N_8Cl_2,H_2O$ requires C, 45·9; H, 4·3; N, 14·0%) (yield, 4·5 g.).

By deacetylation of this material with methanolic sodium methoxide 6-*amino*-4-D-*glucosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine* was obtained. Recrystallised from ethanol–pyridine it had m. p. 225° (decomp.) (Found: C, 42·9; H, 4·0; N, 18·8. $C_{16}H_{18}O_5N_8Cl_2$ requires C, 43·1; H, 4·0; N, 18·9%). The same compound was also obtained by purification of the crude material from the coupling reaction described above.

5 : 6-*Diamino*-4-*tetra-acetyl*-D-*glucosidaminopyrimidine*.—The acetylated azo-compound (0·5 g.) dissolved in ethyl acetate was hydrogenated in presence of Raney nickel during 7 hours at 100°/100 atmospheres. The catalyst was removed by filtration, washed with ethanol, and filtrate and washings evaporated under reduced pressure. Recrystallisation of the residue from ethyl acetate gave the *product* as clusters of needles, which softened at 80° but had no characteristic m. p. (Found: C, 47·0; H, 5·6; N, 15·2. $C_{18}H_{25}O_9N_5$ requires C, 47·5; H, 5·5; N, 15·4%). For preparation of larger quantities the crude hydrogenation product was freed from 2 : 5-dichloroaniline by dissolving it in ethyl acetate and adding light petroleum. The precipitated material was collected and washed with light petroleum and was then sufficiently pure for use in the preparation of 9-D-glucopyranosidoadenine.

9-D-*Glucopyranosidoadenine*.—(a) *From* 9-D-*glucopyranosido*-2-*methylthioadenine*. The 2-methylthio-compound (170 mg.) was acetylated with pyridine and acetic anhydride in the usual manner, giving the acetyl derivative as a resin, which was dissolved in ethanol (42 c.c.) and heated under reflux for 2 hours with Raney nickel (2·5 g.) prepared according to Mozingo (*J. Amer. Chem. Soc.*, 1943, **65**, 1013). After 24 hours the solution was filtered and the residual nickel extracted with boiling ethanol (Soxhlet). Filtrate and extracts were combined and evaporated, and the residue dissolved in methanolic ammonia (30 c.c. saturated at 0°) and kept for 3 days. Solvents were then removed under reduced pressure, the residue dissolved in water, and the solution filtered from a little insoluble material and treated with saturated aqueous picric acid. On cooling, adenine glucoside picrate separated as needles (103 mg.), m. p. 246° (decomp.) alone or mixed with a specimen prepared by Fischer and Helferich's method (Found: C, 38·8; H, 3·5; N, 21·6. Calc. for $C_{11}H_{15}O_5N_5,C_6H_3O_7N_3$: C, 38·8; H, 3·4; N, 21·3%)

(b) *From* 5 : 6-*diamino*-4-D-*glucosidaminopyrimidine*. Crude diamino-compound [from hydrogenation of 0·5 g. of 6-amino-4-tetra-acetyl-D-glucosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine] was dissolved in ethyl acetate (40 c.c.) and shaken for 24 hours with dry dithioformic acid (from 5 g. of $NaS{\cdot}CHS,6H_2O$). Unchanged acid was then filtered off and washed with ethyl acetate, and filtrate and washings evaporated to small volume and passed through a column of neutral activated aluminium oxide (20 g.). The column was washed successively with ethyl acetate (30 c.c.), chloroform (30 c.c.), and dry pyridine (70 c.c.), and the pyridine eluate evaporated to dryness under reduced pressure. The dry resin (168 mg.) was heated under reflux for 3 hours in absolute ethanol (12 c.c.) containing sodium methoxide (18·2 mg.), a slow current of nitrogen being passed through the solution. The residue left by evaporation of the resulting solution under reduced pressure was dissolved in water, neutralised with 0·1N-sulphuric acid, and the solution treated with saturated aqueous picric acid. 9-D-Glucopyranosido-adenine picrate (100 mg.) separated as needles, m. p. 245° (decomp.) alone or in admixture with authentic material (Found: C, 39·1; H, 3·6; N, 21·4%).

We are indebted to the National University of Ireland for the award of a Travelling Fellowship which enabled one of us (A. H.) to participate in this investigation.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 4th*, 1947.]

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185. *Experiments on the Synthesis of Purine Nucleosides. Part XIX. A Synthesis of Adenosine.*

By J. DAVOLL, B. LYTHGOE, and A. R. TODD.

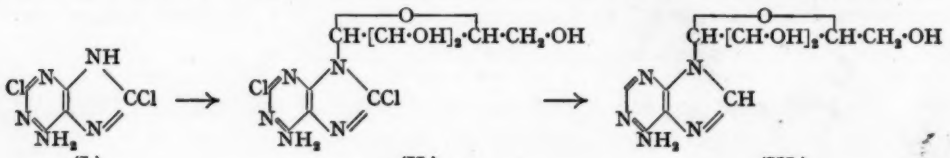
Condensation of the silver salt of 2 : 8-dichloroadenine with crude acetochloro-D-ribofuranose, followed by deacetylation, gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine*. On hydrogenation with a palladised barium sulphate catalyst this compound yielded 9-β-D-*ribofuranosidoadenine*, identical with the natural nucleoside adenosine.

ALTHOUGH our main efforts as described in previous papers of this series have been directed to the development of a general synthetic route for the synthesis of purine nucleosides from appropriate 4-glycosidaminopyrimidines, we have also devoted some attention to other routes which might be of value in individual cases. The method employed by Fischer and Helferich (*Ber.*, 1914, **47**, 210) for the synthesis of adenine glucoside offers one such route, since it has been confirmed that the glucose residue in the synthetic glucoside and the ribose residue in the natural nucleoside adenosine are both located at N_9 in the purine nucleus (Lythgoe, Smith, and Todd, *J.*, 1947, 355; Holland, Lythgoe, and Todd, preceding paper), as was earlier postulated on absorption-spectrum evidence (Gulland and Holiday, *J.*, 1936, 765), and since we have shown that both glycosides have the same configuration (almost certainly β) at the glycosidic linkage (Davoll, Lythgoe, and Todd, *J.*, 1946, 833; Howard, Kenner, Lythgoe, and Todd, *ibid.*, p. 861). The adaptation of this route to the synthesis of adenosine has been studied and had in fact been

successful before various difficulties encountered in the application of our general procedure to the same end have been surmounted. Since the result represents the first recorded synthesis of a naturally occurring purine nucleoside, it is desirable that it be recorded at this stage.

As originally described by Fischer and Helferich (*loc. cit.*) the method was not very attractive, but modifications recently introduced (Davoll, Lythgoe, and Todd, *loc. cit.*) have rendered the preparation of the necessary intermediate 2 : 8-dichloroadenine (I) comparatively simple and so removed one of its main drawbacks. Elsewhere we have described the preparation of acetobromo-D-ribofuranose, and have employed it to effect the first synthesis of the natural pyrimidine nucleoside, cytidine (Howard, Lythgoe, and Todd, *J.*, 1947, 1052). Although the configuration at C_1 in this compound has not been determined, the fact that it yielded cytidine (3-β-D-ribofuranosidocytosine) when condensed with 2 : 4-diethoxypyrimidine and the product treated with ammonia, and that it was also used to prepare 7-β-D-ribofuranosidotheophylline (Howard, Lythgoe, and Todd, *loc. cit.*), encouraged the belief that it, or the corresponding chloro-compound, would react with the silver salt of 2 : 8-dichloroadenine to yield a β-glycoside from which adenosine might be prepared. In view of the great ease with which acetobromoribofuranose loses hydrogen bromide, it was decided that the reaction would be better carried out with the corresponding acetochloro-sugar, which, if rather less reactive, is more stable and therefore more likely to give clean reaction products. 1 : 2 : 3 : 5-Tetra-acetyl-D-ribofuranose was treated with dry ethereal hydrogen chloride, and the crude syrupy acetochloro-D-ribofuranose at once refluxed in xylene solution with 2 : 8-dichloroadenine silver. Deacetylation of the product gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine* (II) in good yield; the stereochemical configuration of (II) was deduced from the fact that on titration with sodium metaperiodate it yielded the same fission product as 2 : 8-dichloro-9-β-D-glucopyranosidoadenine. Hydrogenation of (II) in aqueous sodium hydroxide in presence of a palladised barium sulphate catalyst replaced the halogen atoms by hydrogen and yielded 9-β-D-*ribofuranosidoadenine* (III), identical with a specimen of adenosine prepared from yeast ribonucleic acid by the method of Bredereck, Martini, and Richter (*Ber.*, 1941, **74**, 694). The identity of the two materials was established by m. p. and mixed m. p., optical rotation, periodate titration, and a comparison of *X*-ray powder photographs. Further confirmation was obtained by preparation of their picrates, which were identical in m. p. and mixed m. p.

The synthesis described provides final confirmation of the structure allotted to adenosine and to inosine (9-β-D-ribofuranosidohypoxanthine) which can be prepared from it by deamination. It is, of course, evident that an extension of the synthetic method along the lines used by Fischer and Helferich (*loc. cit.*) in their preparation of guanine glucoside should yield the natural nucleoside guanosine; experiments to this end will be reported upon later.



(I.) (II.) (III.)

Experimental.

Acetochlororibofuranose.—1 : 2 : 3 : 5-Tetra-acetyl-D-ribofuranose (2·5 g.; Howard, Lythgoe, and Todd, *loc. cit.*) was dissolved in dry ethereal hydrogen chloride (50 c.c. saturated at 0°) and the solution set aside at 0° for 3 days. Solvent was removed under reduced pressure and the residue evaporated thrice with dry benzene from a bath at 15°. The product was a colourless syrup which was not further purified but was used immediately for the following experiment.

2 : 8-*Dichloro*-9-β-D-*ribofuranosidoadenine.*—The above crude acetochlororibose was dissolved in dry xylene (10 c.c.) and added to an azeotropically dried suspension of the silver salt of 2 : 8-dichloroadenine (3·5 g.) in xylene (80 c.c.). The mixture was refluxed during 5½ hours with exclusion of moisture, then filtered hot from silver chloride, and light petroleum (350 c.c. of b. p. 40—60°) added to the cooled filtrate. The powdery precipitate produced was collected, washed with light petroleum, then warmed with ethanol (35 c.c.) and allowed to cool. The triacetyl riboside was thus obtained as small buff-coloured crystals (1·82 g., 50%).

The triacetyl compound was dissolved in dry methanol (80 c.c.), cooled to 0°, methanolic ammonia (100 c.c. saturated at 0°) added, and the mixture set aside overnight at 0°. Evaporation of the solution followed by recrystallisation of the residue from water (charcoal) gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine* (0·93 g.) as colourless needles, m. p. 232° (decomp.) (Found in material dried at 140°: C, 36·1; H, 3·6; N, 20·2. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·8; H, 3·3; N, 20·8%).

Periodate Titrations.—(a) 2 : 8-*Dichloro*-9-β-D-*ribofuranosidoadenine.* Sodium metaperiodate (2 c.c. of 0·2663M) was added to a suspension of the glycoside (0·0743 g.) in water (total volume, 10 c.c.) and the

mixture allowed to stand at room temperature till solution was complete (20 hours). Titration of an aliquot portion with standard sodium arsenite showed that the periodate uptake corresponded to 1 mol./mol. of glycoside, and this uptake was unchanged after a further 24 hours. The solution obtained on periodate fission had $\alpha_D^{14°} + 0{\cdot}400°$ ($l = 2$ dm.), from which it can be deduced that the fission product had $[M]_D^{14°} + 9050°$.

(b) 2 : 8-*Dichloro*-9-β-D-*glucopyranosidoadenine*. The glycoside (0·0998 g.; Davoll, Lythgoe, and Todd, *loc. cit.*) was treated with sodium metaperiodate (5 c.c. of 0·2663M) in the same way as the above riboside. The final uptake of periodate after 42 hours was equivalent to 2·03 mols./mol. and the neutralised solution (2 c.c. of fission solution + 1·09 c.c. of N/20-sodium hydroxide) had $\alpha_D^{14°} + 0{\cdot}323°$ ($l = 2$ dm.), corresponding to $[M]_D^{14°} + 9160°$ for the fission product, in close agreement with the value obtained under (a) above.

9-β-D-*Ribofuranosidoadenine* (*Adenosine*).—2 : 8-Dichloro-9-β-D-ribofuranosidoadenine (0·6 g.) was dissolved in water (100 c.c.) and aqueous sodium hydroxide (4 c.c. of N), together with palladised barium sulphate (1 g. of material prepared from 22 g. barium sulphate and 1·8 g. palladous chloride). The mixture was shaken with hydrogen at room temperature for 7 hours; absorption of hydrogen had then ceased (total uptake 90 c.c.). After removal of catalyst by filtration the solution was exactly neutralised to phenolphthalein with hydrochloric acid (5·6 c.c. of 0·1N, corresponding to production of 3·44 millimoles of hydrogen chloride in the reduction; calc., 3·59 millimoles).

The neutralised filtrate was evaporated to dryness under reduced pressure and the residue dissolved in hot water (4 c.c.) and set aside. The crystalline product (0·32 g., 66%) was twice recrystallised from water, and then had m. p. 234—235°. In admixture with natural adenosine (m. p. 233—234°) the m. p. was 233—234° (Found in material dried at 110°: C, 45·2; H, 4·7; N, 26·6. $C_{10}H_{13}O_4N_5$ requires C, 45·0; H, 4·9; N, 26·2%).

The anhydrous synthetic product had $[\alpha]_D^{9°} - 58{\cdot}2°$ (*c*, 0·658 in water; $l = 2$ dm.), while the natural nucleoside had $[\alpha]_D^{11°} - 61{\cdot}7°$ (*c*, 0·706 in water; $l = 2$ dm.). On periodate titration the synthetic product (0·0263 g.) absorbed 1·1 mol. of oxidant/mol. giving a solution the optical rotation of which corresponded to $[M]_D^{9°} - 8700°$ for the fission product. Davoll, Lythgoe, and Todd (*loc. cit.*) have recorded $[M]_D^{19°} - 8560°$ for the periodate fission product of natural adenosine. The *X*-ray powder photographs of anhydrous natural and synthetic adenosine were examined in the Department of Crystallography in this University and found to be identical.

For further confirmation, the synthetic nucleoside was converted into the picrate which had m. p. 180—185° (decomp.) alone or mixed with authentic adenosine picrate [m. p. 180—185° (decomp.)] (Found in material dried at 110°: C, 38·5; H, 3·1; N, 23·0. Calc. for $C_{10}H_{13}O_4N_5,C_6H_3O_7N_3$: C, 38·7; H, 3·2; N, 22·6%).

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance (held by J. D.) and to Roche Products Ltd. for gifts of material.

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186. *Measurement of Specific Surfaces of Calcined and Hydrated Alumina Powders by Adsorption of* n-*Heptoic Acid from Aqueous Solutions.*

By L. SAUNDERS.

The adsorption of *n*-heptoic acid from dilute aqueous solutions by calcined and hydrated alumina powders, the surfaces of which have been freed from soluble alkali, has been examined by means of the surface-tension balance.

The ratio of weight of acid adsorbed to weight of adsorbent is constant for considerable variation of experimental conditions, indicating the formation of an adsorbed layer of definite structure.

This being assumed to be a unimolecular, oriented, condensed layer, the minimum area per acid molecule is 20·5 sq. A. From this, minimum values of the true specific surfaces of the powders can be calculated.

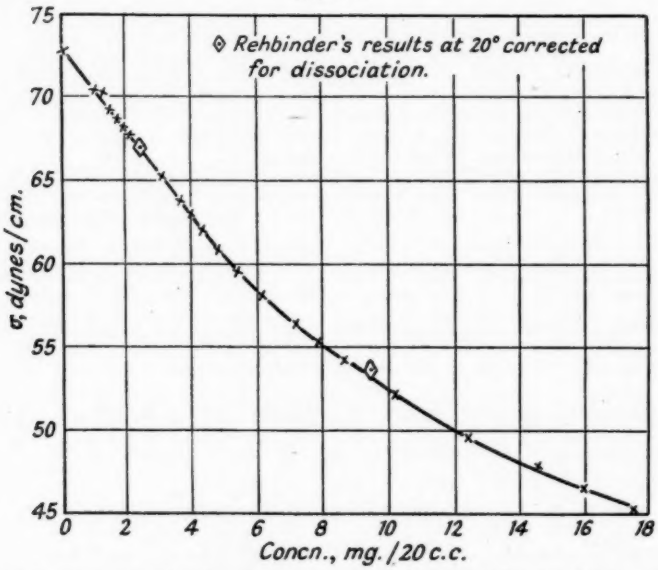
A LARGE number of adsorption methods for the determination of specific surfaces of fine powders have been developed. The disadvantage of many of these is that the adsorbate (*e.g.*, nitrogen, hydrocarbon vapours, dyes) has no particular surface activity, *i.e.*, shows no tendency to spread at an interface to form a unimolecular film. With such adsorbates, the transient formation of a unimolecular film has to be arbitrarily postulated. This difficulty can be overcome by the use of a surface-active adsorbate such as a higher fatty acid. If the carboxyl group affinity of the adsorbent is greater than that of the fluid containing the acid, an adsorbed film will be formed at the fluid–adsorbent interface in which the acid molecules will be oriented with their carboxyl groups towards the powder. In such an oriented film, the acid molecule is likely to occupy an area similar to that in a condensed, oriented film of fatty acid at an air–water interface, *i.e.*, 20·5 sq. A.

Surface-active materials as adsorbates for the measurement of specific surface of powders have been used by Harkins and Gans (*J. Amer. Chem. Soc.*, 1931, **53**, 2804), Ewing (*ibid.*, 1939,

61, 1317), and Smith and Fuzek (*ibid.*, 1946, **68**, 229). In each case non-aqueous solutions of the adsorbates were employed.

It seemed possible that a basic powder such as alumina might adsorb an oriented fatty-acid film from an aqueous solution of the acid. The author has found this to occur when calcined and hydrated alumina powders, the surfaces of which have been freed from soluble alkali, are shaken with dilute aqueous solutions of *n*-heptoic acid. The amount of acid adsorbed can be directly estimated by means of the surface-tension balance and is found to be dependent on the weight and fineness of the powder with which the solution is shaken. The ratio of weight of acid adsorbed to weight of adsorbent is independent of the time of contact of powder and solution provided complete mixing be obtained, it does not vary appreciably with temperature from 10° to 30°, and is independent of the initial concentration of acid solution over a considerable range. It is constant for considerable variation of weight of adsorbent, but decreases if too large a surface area of powder is added to very dilute acid solutions; under these conditions a condensed film of acid is probably not obtained. The constancy of this ratio indicates the formation of a stable adsorbed film of definite structure. It seems likely that this is an oriented, condensed film with an area per acid molecule of 20·5 sq. A. If this is assumed,

FIG. 1.



Surface tension–concentration (corrected for dissociation) : n-heptoic acid in water at 18°.

the absolute value of the specific surface of the powder can be calculated. It is possible that the area per molecule may have the higher value of 25 sq. A., the limiting value for the slightly water-soluble, higher acids at the air–aqueous solution interface (Adam, " Physics and Chemistry of Surfaces ", Oxford Univ. Press, 1941). However, following Harkins and Gans, and Smith and Fuzek, the lower value has been adopted. This gives minimum values for the true specific surfaces of the powders.

These minimum values agree moderately well with those obtained by the air permeability method of Lea and Nurse (*J. Soc. Chem. Ind.*, 1939, **58**, 277) for coarser powders. With fine powders (> 1 sq. m. per g.), the adsorption method gives much higher results, probably owing to the fact that the very fine powders are considerably flocculated in air. The permeability method gives a specific surface corresponding to the mean particle size of the aggregates, whereas the adsorption method measures, in addition, the internal surface of the aggregates giving a specific surface corresponding to the ultimate particle size on which the chemical and catalytic activities of the powder depend.

The amount of heptoic acid adsorbed by alumina powders, free from soluble alkali on the surface, can be measured directly by means of the surface-tension balance. To determine a specific surface, varying weights of powder to produce total surfaces between 0·4 and 2·0 sq. m. are shaken with 20 c.c. of heptoic acid solution (concentration about 4·6 mg./20 c.c.), the mixture

is filtered, and the increase of surface tension ($\Delta\sigma$ dynes/cm.) due to adsorption of acid is found by balancing the filtrate against a sample of the original solution.

The surface tension–concentration curve for aqueous solutions of heptoic acid has been determined in detail at 18° by Sugden's maximum bubble pressure method (Fig. 1). The curve cuts the surface-tension axis at a point above the surface tension of water unless a correction for the dissociation of the acid is made. Using Dippy's value (*J.*, 1938, 1222) of the dissociation constant, $1{\cdot}28 \times 10^{-5}$ at 25°, the initial slope of the curve is only very slightly altered and it now cuts the surface-tension axis at $\sigma = 72{\cdot}9$. The curve is linear for acid concentrations less than 5 mg./20 c.c. The slope of this initial portion is 2·49 dynes/cm. per mg./20 c.c. From Rehbinder's results (*Z. physikal. Chem.*, 1924, **111**, 447), corrected for dissociation, the following values of this initial slope have been calculated: at 0°, 10°, 20°, and 40°, 3·21, 2·75, 2·37, and 1·67 dynes/cm. per mg./20 c.c. The temperature coefficient in the vicinity of 18° is − 0·04 per °c.

In a recent paper on the surface tension of aqueous solutions of the higher fatty acids, Douglas and Mackay (*Canadian J. Res.*, 1946, **24***A*, 8) describe measurements made by Ferguson and Hakes's modification of the capillary-rise method (*Proc. Physical Soc.*, 1929, **41**, 214). They erroneously state that it is unnecessary to determine contact angles when this method is used. They also employ a Pyrex capillary which is far more likely to produce a contact angle with the acid solutions than a soda-glass tube. A plot of their results of lowering of surface tension of water by heptoic acid against concentration of acid (taking the I.C.T. value of 0·29% by weight as the saturation concentration of heptoic acid in water at 20°, as they express their concentrations as fractions of the saturation value) gives an irregular curve. These irregularities are due to the incidence of a contact angle between the heptoic acid solution and the Pyrex capillary. When a liquid does not completely wet the capillary, *i.e.*, has a contact angle on it, Ferguson and Hakes's method of measuring surface tension cannot be used, for the meniscus tends to stick in the capillary and its movement is not sensitive to small changes of pressure.

If $\Delta\sigma$ dynes/cm. is the increase of surface tension produced by shaking M g. of alumina powder with 20 c.c. acid solution (concentration <5 mg./20 c.c.), we have

$$\text{Weight of acid adsorbed} = x = \frac{\Delta\sigma}{2{\cdot}49 - 0{\cdot}04t}\ \text{mg.} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

t is the amount by which the temperature of the solutions exceeds 18° at the time of balancing. (It is important that the two solutions should be at the same temperature when the balance point is determined.)

In a unimolecular, condensed film the acid occupies an area per molecule of $20{\cdot}5 \times 10^{-16}$ sq. cm., *i.e.*, 1 mg. of acid occupies 0·95 sq. m.

$$\text{Specific surface of powder} = 0{\cdot}95 \times x/M\ \text{sq. m./g.} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Thus the specific surface is simply related to the experimentally determined quantities $\Delta\sigma$ and M.

The accuracy of the specific surface determinations is considered to be $\pm$ 10%.

Experimental.

Before carrying out a specific surface determination, it is essential to remove soluble alkali from the powder surface, as this gives high results owing to neutralisation of the acid. The author has found that no further appreciable extraction of soluble alkali occurs after 4 hours' vigorous extraction of small samples of commercial alumina powders with boiling distilled water in a Soxhlet apparatus. The acid-insoluble, calcined alumina can be extracted with boiling, dilute hydrochloric acid. After extraction, the powders are dried at 110°. In some cases, the powders cake on drying, but this loose aggregation does not affect the value for specific surface found by this method.

n-Heptoic acid was obtained from B.D.H. On fractional distillation, nearly all the sample came over between 117° and 118°/13 mm. (cf. b. p. 117·5°/13 mm. from Pool and Ralston's results, *Ind. Eng. Chem.*, 1942, **34**, 1104). This fraction had b. p. 222°/760 mm. (cf. Pool and Ralston, 223°). The surface tensions of aqueous solutions of the distilled acid showed no appreciable differences from those of the undistilled material.

The surface-tension balance is a modification of that described by Warren (*Phil. Mag.*, 1927, **4**, 358). A Sugden maximum bubble pressure surface-tension apparatus (Adam, *op. cit.*), is joined by a Y-tube to a similar apparatus having identical tube tip dimensions, and to an air pressure line incorporating a water manometer. It is a great advantage to have an all-glass assembly as this eliminates clogging of the capillaries by crumbs and dust from rubber tubing. The wide bubbling tubes are of 3-mm. soda-glass; the identical capillaries are made by drawing out a piece of 3-mm. soda-glass tubing and cutting it carefully in the centre. The ease of operation and reliability of the balance depend entirely on the shape of the capillaries. They should taper continuously to the orifice with as short a constricted portion as possible, the wall at the tube tip should be thin, and the radius of the orifice should be about 0·1 mm. To obtain all these desirable properties in one pair of capillaries requires some practice.

The two apparatuses are calibrated separately with water and benzene, and the constants, A and B' determined for the empirical equation relating surface tension σ (in dynes/cm.) of a liquid to the difference in maximum pressures required to blow bubbles on the narrow (h_n) and the wide (h_w) tube when they are immersed to the same depth in the liquid (of density d):

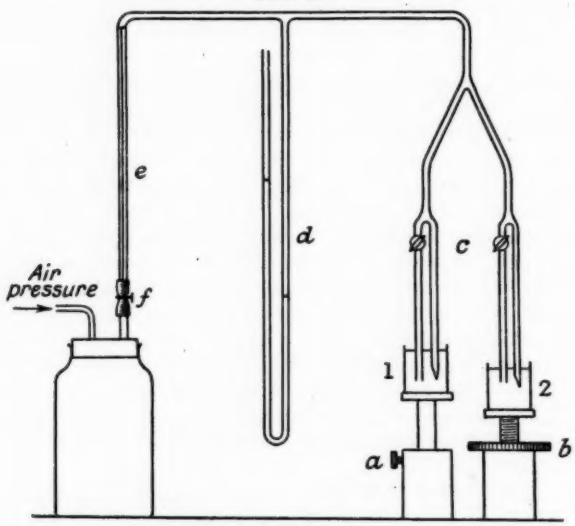
$$A(h_n - h_w + Bd) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

h_n and h_w are pressures in cm. of water at 18°.

The value of B is mainly dependent on the radius of the wide tube and is small compared with $(h_n - h_w)$. The identical tube tip dimensions are found to result in identical values of A and B.

To measure the difference of surface tensions of two heptoic acid solutions, they are placed in the beakers 1 and 2 as shown in Fig. 2. The taps to the wide tubes are closed and a rapid

FIG. 2.



Surface tension balance.

1, 2. *Beakers containing solutions.*
a. Clamping screw for coarse adjustment of balance point.
b. Milled wheel for fine adjustment.
c. Taps to cut off wide tubes.
d. Water manometer.
e. Capillary tubing.
f. Screw clip to adjust bubble rate.

stream of air is blown through the capillaries for several minutes; the stream is then reduced so that the capillaries bubble at a rate of about 1 per sec. The height of beaker 2 is adjusted until bubbles form alternately on the two capillaries. This balance point can be very sharply determined. At the balance point

$$\left.\begin{aligned} {}^1h_n &= {}^2h_n \\ \sigma_2 &= A({}^2h_n - {}^2h_w + B) \\ \sigma_1 &= A({}^1h_n - {}^1h_w + B) \end{aligned}\right\} \text{from equation (3) with } d = 1$$

$$\sigma_2 - \sigma_1 = A({}^1h_w - {}^2h_w)$$

$$\Delta\sigma = A \,.\, \Delta h \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The difference in surface tension is therefore proportional to the difference in maximum pressures required to blow bubbles on the two wide tubes at the balance point; ${}^1h_w$ and ${}^2h_w$ are measured on the water manometer by opening the taps separately.

If M g. of alumina powder are shaken with 20 c.c. of heptoic acid solution (concentration <5 mg./20 c.c.) and the filtrate is balanced against the original solution, the two liquids being at the same temperature (18° + t°) at the time of balancing, then from equations (1), (2), and (4):

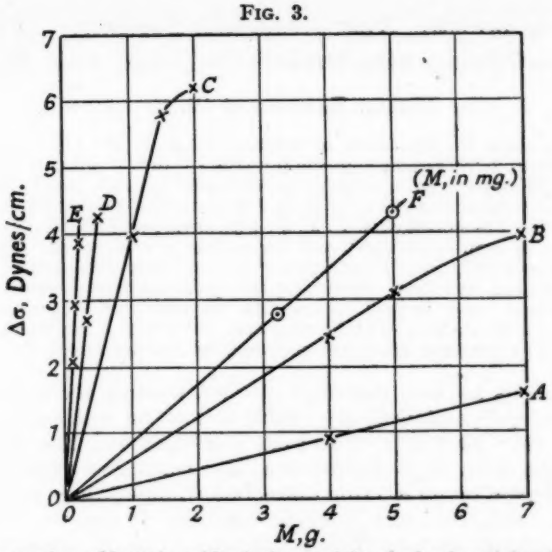
$$\text{Specific surface of powder} = \frac{0{\cdot}95\,A}{2{\cdot}49 - 0{\cdot}04t} \times \frac{\Delta h_w}{M} \text{ sq.m./g.}$$

In practice, the most suitable initial concentration of the heptoic acid solution has been found to be about 4·6 mg./20 c.c. (0·5 c.c. of acid to 2 l. of water). The weights of powder shaken with 20 c.c. of this solution should be such as to produce an adsorbing surface of 0·4—2·0 sq.m.

Grease-free distilled water of high surface tension was used for making up the solutions.

Fig. 3 shows values of $\Delta\sigma$ plotted against M for several alumina hydrate powders. The slopes of these curves are proportional to the specific surfaces of the powders. They indicate the relative inefficiency of ball milling for the production of alumina hydrate powders of high specific surface.

FIG. 3.



Increase of surface tension of heptoic acid solution–weight of adsorbent (alumina hydrate) at 18°.

A.	*Through* 200 *B.S.S.*	0·09 *sq.m./g.*
B.	*Milled* 2 *hrs.*	0·24 *sq.m./g.*
C.	*Milled* 8 *hrs.*	1·5 *sq.m./g.*
D.	*Milled* 92 *hrs.*	3·4 *sq.m./g.*
E., *F.*	*Specially prepared chemically to give large surface area*	7·9 *sq.m./g.*, 310·0 *sq.m./g.*

The following tables give further results of measurements.

Specific surface of alumina hydrate powders (in sq. m./g.). *Specific surface of calcined alumina powders.*

	Air permeability.	Adsorption.	Air permeability.	Adsorption.
A	0·09	0·09	0·53	0·76
B	0·18	0·19	0·92	1·04
C	1·00	1·51	0·81	1·64
D	1·05	310	—	—

An *X*-ray pattern for powder D indicated a minimum specific surface of 250 sq. m./g.

Effect of variation of initial concentration of heptoic acid.

Initial concn., mg./20 c.c.	Wt. of adsorbent, *M*, g.	Δσ, dynes/cm.	Wt. of acid adsorbed, *x* (mg.).	*x*/*M*, mg./g.
18·20 *	2·22	0·71	1·00	0·45
	4·15	0·94	1·25	0·30
	7·09	1·42	1·82	0·26
	9·89	1·71	2·18	0·22
9·10 *	1·59	0·59	0·42	0·26
	4·18	1·59	1·04	0·25
	7·71	2·77	1·82	0·24
	10·07	3·30	2·17	0·22
4·55	2·08	1·36	0·56	0·23
	4·21	2·89	1·18	0·26
	7·19	4·48	1·83	0·24
	9·67	5·66	2·31	0·23
2·27	1·94	1·30	0·53	0·27
	3·97	1·83	0·75	0·20
	7·66	2·65	1·13	0·15

* *x* is not directly proportional to Δσ for solutions of concentration greater than 5 mg./20 c.c.

The author wishes to thank the British Aluminium Company for permission to publish this work.

RESEARCH LABORATORIES, BRITISH ALUMINIUM COMPANY LTD.,
CHALFONT PARK, GERRARDS CROSS, BUCKS.

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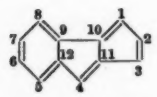
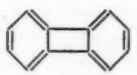
187. *Attempts to prepare New Aromatic Systems. Part I.* cyclo*Pentindene. Phenyl*cyclo*pentanecarboxylic Acids, and Derived Ketones.*

By Wilson Baker and W. G. Leeds.

This paper describes the synthesis of 4-*keto*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*cyclo*pentindene* (III), which is a possible intermediate in the preparation of the unknown aromatic compound *cyclo*pentindene. Benzene and *cyclo*pent-1-enecarboxylic acid react in the presence of aluminium chloride to give a mixture of 2- and 3-phenyl*cyclo*pentane-1-carboxylic acids (IV) and (VI), and 4-*keto*-1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII). The structures of the two acids have been established, and derivatives are described. The acids are readily cyclised to the ketones (III) and (VII) respectively, the latter being a derivative of benz*cyclo*heptane. The confused literature concerning the phenyl*cyclo*pentanecarboxylic acids, their functional derivatives, and related ketones is surveyed and corrected. 2-Benzyl*cyclo*pentanone (XIV) and indan-3-one-1-carboxylic acid (XV), which are possible intermediates in the synthesis of *cyclo*pentindene, have been prepared by improved methods.

Preliminary experiments are now described directed towards the synthesis of the unknown aromatic hydrocarbon *cyclo*pentindene (I), which is isomeric with diphenylene (II) (Lothrop, *J. Amer. Chem. Soc.*, 1941, **63**, 1187). This work was begun at a time when it seemed possible that diphenylene might really be *cyclo*pentindene, but conclusive evidence that diphenylene is (II) has since been afforded by (*a*) electron diffraction studies (Waser and Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 1451), (*b*) ready catalytic reduction to diphenyl (Baker, *J.*, 1945, 265), (*c*) *X*-ray crystallographical analysis (Waser and Chia-Si Lu, *J. Amer. Chem. Soc.*, 1944, **66**, 2035). The name *cyclo*pentindene was suggested for (I) by Patterson and Capell (" The Ring Index ", 1940, p. 204), and (I) may also be termed " benzopentalene ", " pentalene " (*idem*, *ibid.*, p. 110) being the unknown hydrocarbon, C_8H_6, consisting of two fused *cyclo*pentadiene rings.

(I.) 

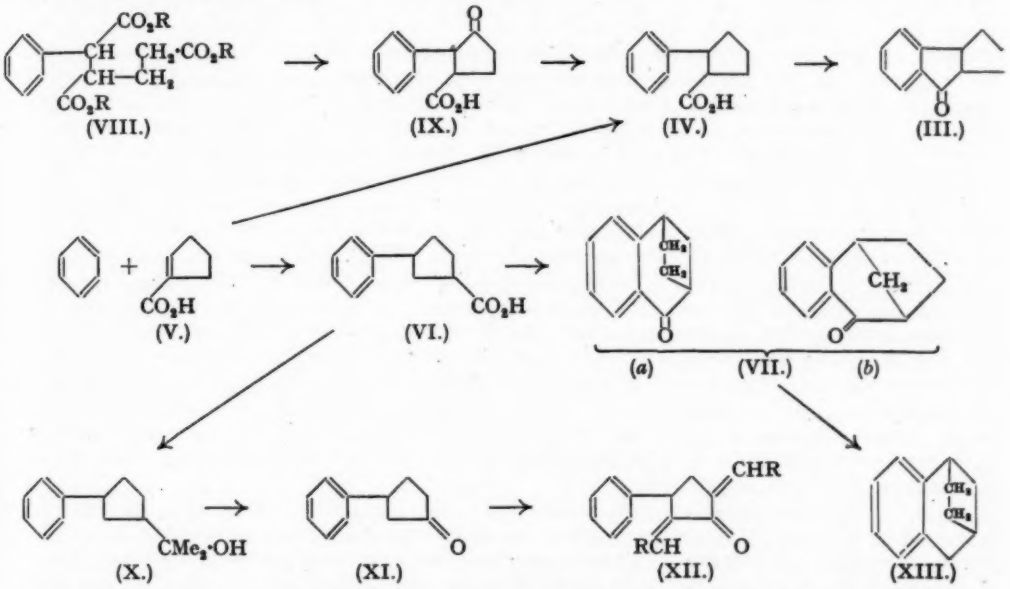
 (II.)

Pentalene was first postulated as a possible aromatic compound by Armit and Robinson (*J.*, 1922, **121**, 828), and unsuccessful attempts were made to prepare it by dehydrogenation of its octahydro-derivative (Barrett and Linstead, *J.*, 1936, 612; see also Baker, *loc. cit.*). The only known derivatives of pentalene are the complex diphenyl and dichloro-derivatives of 1 : 2 : 4 : 5-dibenzpentalene (2 : 3-benz*cyclo*pentindene) (Brand, *Ber.*, 1912, **45**, 3071; Brand and Ludwig, *ibid.*, 1920, **53**, 809; Brand and Hoffmann, *ibid.*, p. 815; Brand and Müller, *ibid.*, 1922, **55**, 601; Brand, Gabel and Ott, *ibid.*, 1936, **69**, 2504; Wawzonek, *J. Amer. Chem. Soc.*, 1940, **62**, 745) which have been termed diphensuccindadienes.

The present work had as its object the synthesis of compounds containing the hexahydro-*cyclo*pentindene system which, by direct or indirect processes of dehydrogenation, might be converted into the fully aromatic type. Of the various routes which were considered, the most direct appeared to be the preparation of 4-*keto*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*cyclo*pentindene* (III) by the cyclisation of 2-phenyl*cyclo*pentane-1-carboxylic acid (IV). The synthesis of this acid, however, has not proved straightforward, and the work has disclosed a number of inaccuracies and misinterpretations in the literature.

A direct synthesis of the acid (IV) appeared to be offered by the addition of benzene to *cyclo*pent-1-enecarboxylic acid (V). This reaction has been investigated by Nenitzescu and Gavât (*Annalen*, 1935, **519**, 260) who reported that, in presence of aluminium chloride, migration of the double bond occurred, giving a liquid 3-phenyl*cyclo*pentane-1-carboxylic acid (VI), the structure of which was proved by independent synthesis from 1 : 4-dibromo-2-phenylbutane and malonic ester, followed by hydrolysis and decarboxylation. Reinvestigation of this reaction showed, however, that under mild conditions it gives mainly 3-phenyl*cyclo*pentanecarboxylic acid (VI), but at the boiling point of benzene it yields a liquid mixture of 3-phenyl*cyclo*pentanecarboxylic acid (VI), 2-phenyl*cyclo*pentanecarboxylic acid (IV), 4-*keto*-1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII), and a hydrocarbon, probably phenyl*cyclo*pentane. Some specimens of the mixed acids prepared by the latter procedure partially crystallised at 0°, and a solid acid, m. p. 87—88°, was isolated in up to 10% of the total weight of acids. The solid and liquid acids gave very sparingly soluble S-*benzylthiuronium* salts, and by repeated crystallisation of the latter salt the free originally liquid acid has been obtained also in the crystalline state, and has m. p. 17—18·5°. The higher- and lower-melting acids were

characterised as 2-phenyl*cyclo*pentanecarboxylic acid (IV) and 3-phenyl*cyclo*pentanecarboxylic acid (VI) respectively as described in the following paragraphs. Both acids differ from the known racemic 1-phenyl*cyclo*pentane-1-carboxylic acid (Case, *J. Amer. Chem. Soc.*, 1934, **56**, 716) which has m. p. 158—159°.



2-*Phenyl*cyclo*pentane*-1-*carboxylic Acid*, m. p. 87—88°.—Chatterjee (*J. Indian Chem. Soc.*, 1938, **15**, 211) claims to have prepared this acid by an unambiguous but lengthy method and described it as an oil. In view of the great ease of crystallisation of the acid, m. p. 87—88°, it did not seem likely that the two could be identical, but they have, in fact, proved to be so. Repetition of Chatterjee's synthesis, with modifications at intermediate stages but the same final stage, has yielded a crystalline acid, identical with that prepared by the addition of benzene to *cyclo*pent-1-enecarboxylic acid. Chatterjee's method consisted in condensing benzaldehyde cyanohydrin with the sodio-derivative of cyanoacetic ester and then with ethyl β-chloropropionate to give ethyl γδ-dicyano-γ-carbethoxy-δ-phenyl-*n*-valerate, Ph·CH(CN)·C(CN)(CO_2Et)·CH_2·CH_2·CO_2Et, hydrolysing and re-esterifying to give ethyl γδ-dicarbethoxy-δ-phenyl-*n*-valerate (VIII; R = Et), cyclising with sodium to ethyl 2-phenyl-*cyclo*pentan-3-one-1 : 4-dicarboxylate, hydrolysing to 2-phenyl*cyclo*pentan-3-one-1-carboxylic acid (IX), and finally reducing by Clemmensen's method to 2-phenyl*cyclo*pentane-1-carboxylic acid (IV). As both (IV) and (IX) were required in some quantity for later work, a detailed study has been made of Chatterjee's series of reactions and considerable improvements effected. The dicyano-intermediate, ethyl γδ-dicyano-γ-carbethoxy-δ-phenyl-*n*-valerate, is best prepared by condensation of ethyl β-chloropropionate with the sodio-derivative of ethyl αβ-dicyano-β-phenylpropionate, itself formed by the direct addition of sodium cyanide to ethyl benzylidenecyanoacetate. Neither the ethyl benzylidenecyanoacetate nor the ethyl αβ-dicyano-β-phenylpropionate need necessarily be isolated. Hydrolysis and esterification with methyl alcohol gave the *methyl* ester (VIII; R = Me), and this underwent smooth cyclisation in presence of methyl-alcoholic sodium methoxide to the 2-phenyl*cyclo*pentanone derivative.

cis- and *trans*-Forms of 2-phenyl*cyclo*pentane-1-carboxylic acid are possible, and it is not known with certainty which structure represents the acid, m. p. 87—88°. In view, however, of the fact that the acid is readily cyclised to a ketone (see below), it may be assumed provisionally that it is the *cis*-form.

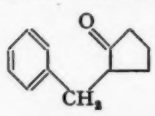
3-*Phenyl*cyclo*pentane*-1-*carboxylic Acid*, m. p. 17—18·5°.—There could be little doubt that this acid, although previously described as a liquid, was identical with the 3-phenyl*cyclo*pentane-1-carboxylic acid of Nenitzescu and Gavât (*loc. cit.*). As, however, a direct comparison of specimens was not possible, the acid was submitted to the Barbier–Wieland degradation, giving, *via* its methyl ester and 3-*phenyl*cyclo*pentyldimethylcarbinol* (X), 3-phenyl*cyclo*pentanone (XI), the position of the carbonyl group, and hence that of the original carboxyl group, being

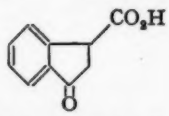
established by the preparation of a dibenzylidene derivative (XII; R = Ph), and a *dipiperonylidene* derivative (XII; R = 3 : 4-methylenedioxyphenyl). The easy cyclisation of the acid (VI) to a ketone (see below) strongly suggests that it is the *cis*-isomeride.

Cyclisation of the phenyl*cyclo*pentanecarboxylic acids (IV) and (VI) is effected smoothly in 85% yield by heating with a mixture of syrupy phosphoric acid and phosphoric anhydride, and gives the liquid ketones, 4-keto-1 : 2 : 3 : 4 : 10 : 11-hexahydro*cyclo*pentindene (III) and 4-keto-1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydronaphthalene (VII*a*); the latter may equally be regarded as the bridged benz*endo*methylene*cyclo*heptenone derivative (VII*b*). The previously mentioned formation of a small amount of the ketone (VII) by the interaction of benzene, *cyclo*pent-1-enecarboxylic acid (V), and aluminium chloride, is explained by the fact that 3-phenyl*cyclo*pentane-1-carboxylic acid (VI) undergoes partial cyclisation to (VII) under the influence of aluminium chloride in boiling benzene. Yields of 20—40% of the ketone (VII) from the acid (VI) have been obtained by the action of phosphorus oxychloride, 80% sulphuric acid, or phosphoric anhydride in toluene, and by the action of stannic chloride on the acid chloride in benzene solution. The easy formation of (VII) opens up the possibility of a new route to the difficultly accessible benzo*cyclo*heptenone series. The ketones were characterised as 2 : 4-*dinitrophenylhydrazones* and as *semicarbazones*. The semicarbazone of (VII) forms well-developed crystals containing half a molecule of solvent of crystallisation from methyl and ethyl alcohols and from toluene. The toluene is readily detected by a micro-modification of Ramsden's test (see experimental section). In addition to the unexplained fact that Chatterjee's 2-phenyl*cyclo*pentane-1-carboxylic acid was an oil, is his curious claim that the related ketone, prepared by cyclisation of the acid chloride with aluminium chloride, gives a semicarbazone, m. p. 170°. We find, however, that the semicarbazone of the ketone (III) melts at 242° and does not contain solvent of crystallisation.

Mention must also be made of the work of von Braun and Kühn (*Ber.*, 1927, **60**, 2557) who described as 2-phenyl*cyclo*pentane-1-carboxylic acid a product prepared by the addition of hydrogen bromide to 1-phenyl*cyclo*pent-2-ene, and conversion of the resulting phenylbromo-*cyclo*pentane into a carboxylic acid *via* the derived Grignard reagent. This acid was an oil, possibly not homogeneous, from which an impure anilide, m. p. 93—95°, was obtained, thus excluding the possibility that their acid was identical with the 2-phenyl*cyclo*pentane-1-carboxylic acid described in this paper, the anilide of which melts at 90—91°. Von Braun and Kühn were able to cyclise their acid to a ketone by treatment of its chloride with aluminium chloride, and dismissed the possibility that the acid might be 3-phenyl*cyclo*pentane-1-carboxylic acid on the unjustified assumption that such an acid could not undergo ring closure to a cyclic ketone. It is most probable that the acid described by von Braun and Kühn was at least mainly 3-phenyl*cyclo*pentane-1-carboxylic acid (VI); this view is consistent with the melting point of their crude anilide, and with the fact that the related ketone gave a semicarbazone, m. p. 170°, from methyl alcohol [the semicarbazone of (VII) has initial m. p. *ca.* 170° when crystallised from methyl or ethyl alcohols—see experimental section], although no mention is made of solvent of crystallisation.

Reduction of (VII) by Clemmensen's method yields the liquid 1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII), which gives a well-crystalline, but incompletely homogeneous *sulphonamido*-derivative. This is probably a mixture of the 6- and 7-sulphonamido-compounds.

(XIV.) 



(XV.)

A number of substances have been prepared as possible intermediates in the synthesis of compounds containing the *cyclo*pentindene skeleton. (a) 2-*Benzyl*cyclo*pentanone* (XIV) has been prepared as follows. Ethyl 1-benzyl*cyclo*pentan-2-one-1-carboxylate is readily prepared by the condensation of benzyl chloride with ethyl *cyclo*pentan-2-one-1-carboxylate in benzene solution in presence of sodium (with alcoholic sodium ethoxide the same reactants yield diethyl α-benzyladipate; Duff and Ingold, *J.*, 1934, 87), and hydrolysis with hydrochloric acid then yields 2-benzyl*cyclo*pentanone. This synthesis of 2-benzyl*cyclo*pentanone is more direct than that of Duff and Ingold (*loc. cit.*), who hydrolysed diethyl α-benzyladipate, and converted it into the ketone *via* the anhydride. (b) 2-*Acetonyl*-1 : 3-*diketoindane* is produced in small yield by the condensation of monochloroacetone with 1 : 3-diketoindane in presence of alcoholic sodium ethoxide. (c) Indan-3-one-1-carboxylic acid (XV) is available in 61% yield from phenylsuccinic acid by reaction with thionyl chloride followed by treatment with aluminium

chloride in nitrobenzene. Cyclisation of phenylsuccinic acid was achieved in 22% yield by Speight, Stevenson, and Thorpe (*J.*, 1924, **125**, 2190) by the use of concentrated sulphuric acid. The related *ethyl* ester and *amide* are described, and a *compound*, probably either ethyl 2-acetylindan-3-one-1-carboxylate or ethyl β-keto-β-(3-keto-1-indanyl)propionate, prepared from the former by reaction with ethyl acetate in presence of sodium ethoxide.

Experimental.

Reaction of Benzene with cyclo*Pent*-1-*enecarboxylic Acid.*—*cyclo*Pent-1-enecarboxylic acid was prepared according to Cook and Linstead (*J.*, 1934, 958), but difficulty was experienced with emulsions in extracting the corresponding nitrile prepared by the dehydration of *cyclo*pentanone cyanohydrin. This difficulty is avoided and the yield of pure nitrile increased by first steam-distilling the reaction product, extracting it with benzene, and then distilling it in a vacuum. A solution of *cyclo*pent-1-enecarboxylic acid (35 g., 1 mol.) in benzene (700 c.c.) was placed in a 3-l. three-necked flask fitted with reflux condenser and mercury-sealed stirrer. Powdered anhydrous aluminium chloride (135 g.; 3 mols., optimum quantity) was added during 30 minutes while cooling in ice. Stirring was continued for 1 hour at room temperature and for a further hour at 50°. After 20 hours at room temperature the product was poured on crushed ice and concentrated hydrochloric acid, most of the benzene removed in steam, and the liquid shaken with ether. The ethereal extract was shaken with excess of 15% aqueous sodium hydroxide, the ether layer separated, the alkaline layer acidified, and the oily product again extracted with ether, the extracts dried and distilled, giving slightly crude 3-phenyl*cyclo*pentane-1-carboxylic acid (VI) as a viscous oil, b. p. 154—156°/0·9 mm. (50·6 g.; 85% yield) (Found: equiv., 191. Calc. for $C_{12}H_{14}O_2$: equiv., 190). When less than 2·5 mols. of aluminium chloride are used, unchanged *cyclo*pent-1-enecarboxylic acid is found in the reaction product.

When the reaction was carried out at the b. p. of the benzene, the yield of acidic product was somewhat diminished, and, in addition, there was isolated non-acidic material (2·2 g., b. p. 100—200°/20 mm.) which proved to be a mixture containing 4-*keto*-1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII) and a hydrocarbon, probably phenyl*cyclo*pentane. These were separated by refluxing the mixture in alcoholic solution for 3 hours with excess of Girard T reagent and acetic acid, pouring the resulting mixture into dilute sodium carbonate solution at 0°, extracting the hydrocarbon with ether, and regenerating the ketone by hydrolysis with hydrochloric acid for 2 hours on the water-bath. The hydrocarbon was freed from the last traces of ketone by a further similar treatment with Girard T reagent, and was obtained after fractionation as an oil, b. p. 115°/19 mm. (lit., b. p. 116—117°/37 mm.) (Found: C, 90·0; H, 10·3. Calc. for $C_{11}H_{14}$: C, 90·3; H, 9·7%). The regenerated ketone (b. p. 166—169°/21 mm.; $n_D^{20°}$ 1·578) gave a 2 : 4-*dinitrophenylhydrazone*, crystallising from acetic acid in red needles, m. p. 240—242°, and 242—244° when mixed with the 2 : 4-dinitrophenylhydrazone of the ketone prepared by cyclisation of 3-phenyl*cyclo*pentane-1-carboxylic acid (VI) (see below).

2-*Phenyl*cyclo*pentane*-1-*carboxylic Acid* (IV).—Several samples of the acid which had been prepared at the b. p. of the benzene partially crystallised when kept at 0°. The separated 2-phenyl*cyclo*pentane-1-carboxylic acid crystallised from light petroleum (b. p. 60—80°) in boat-shaped plates, m. p. 87—88° (yield up to 10% of the weight of the mixed acids) (Found: C, 75·5; H, 7·4. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%). The acid (IV) (1 g.) was exactly neutralised by N-sodium carbonate, and a solution of *S*-benzylthiuronium chloride (1 g.) in water (30 c.c.) added. The precipitated S-*benzylthiuronium* salt was collected, washed with water, dried, and crystallised rapidly twice from alcohol, being obtained in thin plates, m. p. 165° (fairly rapid heating) (Found: N, 7·8. $C_{12}H_{14}O_2,C_8H_{10}N_2S$ requires N, 7·9%).

3-*Phenyl*cyclo*pentane*-1-*carboxylic Acid* (VI).—The liquid acid (20 g.) which either failed to solidify or remained after the separation of the solid acid was converted into its S-*benzylthiuronium* salt in the manner described above. After crystallising rapidly first from 50% alcohol (1 litre) and then three times from alcohol it formed elongated plates, m. p. 169° (fairly rapid heating; conditions the same as above), depressed to 150° on admixture with the isomeric salt (Found: N, 7·8. $C_{12}H_{14}O_2,C_8H_{10}N_2S$ requires N, 7·9%). The 3-phenyl*cyclo*pentane-1-carboxylic acid (VI), after regeneration from this purified salt, distilled at 137—138°/0·2 mm. ($d_{18°}^{18°}$ 1·108; $n_D^{20°}$ 1·5423), and crystallised on cooling to a solid, m. p. 17—18·5° (Found: C, 75·7; H, 7·4. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%). The solubility of the acid (IV) in the pure acid (VI) at 15° is *ca.* 30 parts of (IV) to 100 parts of (VI).

Amide and Anilide of 3-*Phenyl*cyclo*pentane*-1-*carboxylic Acid* (VI).—The acid (6·8 g.) and thionyl chloride (6 c.c.) were heated for 1 hour at 70—75°; distillation then gave the acid *chloride* (6·6 g.) as a pungent, faintly yellow oil, b. p. 163°/20 mm. (Found: Cl, 17·3. $C_{12}H_{13}OCl$ requires Cl, 17·0%), converted by shaking with concentrated aqueous ammonia into the amide, which crystallised from ethylene chloride or water in very thin, almost rectangular, nacreous plates, m. p. 147—148° (Found: C, 75·8; H, 7·9; N, 7·5. Calc. for $C_{12}H_{15}ON$: C, 76·2; H, 8·0; N, 7·4%). The anilide, obtained by treating the acid chloride in dry ether with excess of aniline for 1 hour, is difficult to purify; it was crystallised twice from carbon tetrachloride–light petroleum (b. p. 40—60°), and finally from benzene–light petroleum (b. p. 60—80°) and obtained in minute plates, m. p. 106—107° (Found: C, 81·8; H, 7·5; N, 5·5. Calc. for $C_{18}H_{19}ON$: C, 81·5; H, 7·2; N, 5·3%).

Amide and Anilide of 2-*Phenyl*cyclo*pentane*-1-*carboxylic Acid* (IV).—These derivatives were prepared and crystallised in the same way as the corresponding isomerides. 2-*Phenyl*cyclo*pentane*-1-*carboxyamide* formed long needles, m. p. 146—147° (Found: C, 76·1; H, 7·9; N, 7·6. $C_{12}H_{15}ON$ requires C, 76·2; H, 8·0; N, 7·4%); the mixed m. p. with the 3-phenyl isomeride was *ca.* 115—125°. 2-*Phenyl*cyclo*pentane*-1-*carboxyanilide* formed fine prisms, m. p. 90—91° (Found: C, 81·7; H, 7·2; N, 5·7. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

Ethyl αβ-Dicyano-β-phenylpropionate.—To benzaldehyde (53 g.; 1 mol.) and cyanoacetic ester (56·5 g.; 1 mol.) in alcohol (100 c.c.) was added piperidine (2 c.c.), and the mixture rapidly warmed so

that the maximum temperature attained was 60°, left for 1 hour, and finally shaken under the tap (the condensation is exothermic); benzylidenecyanoacetic ester then crystallised. Powdered sodium cyanide (35 g.) was added and the mixture heated for 5 minutes on the water-bath, by which time the marked yellow colour had faded. The cooled mixture was treated with a solution of sodium hydroxide (20 g.) in water (500 c.c.), extracted with ether (250 c.c.), the aqueous layer acidified with concentrated hydrochloric acid (100 c.c.), and while warm a rapid current of air blown through it to remove ether and hydrogen cyanide. The solid product (seeding was sometimes required) was collected after cooling in ice, washed, and dried at a moderate temperature (yield 100 g.). The compound is difficult to crystallise, but the following method succeeds well. The crude material (100 g.) was dissolved in warm methyl alcohol (640 c.c.), and, after addition of water (300 c.c.), treated with charcoal and filtered. To the filtrate was added a little methyl alcohol to give a solution just clear at 30°. The solution was then seeded, cooled while shaking, and finally placed in the ice-chest. The solid was collected, washed with ice-cold 50% methyl alcohol (100 c.c.), and dried (yield 80·3 g.; m. p. 63—65°). The pure compound has m. p. 65° (cf. Baker and Lapworth, *J.*, 1925, **127**, 563).

γδ-Dicarboxy-δ-phenyl-n-valeric Acid (VIII; R = H).—(a) *From ethyl αβ-dicyano-β-phenylpropionate.* To a cooled solution of sodium (9·2 g.) in absolute alcohol (400 c.c.) was added ethyl αβ-dicyano-β-phenylpropionate (91·2 g.; 1 mol.) and β-chloropropionic ester (60 g.; 1·1 mol.), and the mixture refluxed for 6 hours, after which the solvents were removed under diminished pressure. The remaining oily product was hydrolysed by refluxing it for 18 hours with concentrated hydrochloric acid (500 c.c.) and water (100 c.c.). Boiling water (400 c.c.) and charcoal (5 g.) were added, the liquid filtered (sintered glass) hot, and the charcoal washed with boiling water (100 c.c.). After thorough cooling the acid was collected, washed, and dried; yield 91·5 g.; m. p. 178—180°.

(b) A mixture of benzaldehyde (53 g.), cyanoacetic ester (56·5 g.), alcohol (200 c.c.), and piperidine (2 c.c.) was warmed to 60°; after 1 hour powdered sodium cyanide (25 g.; 1 mol.) was added and the mixture shaken whilst being heated on the water-bath for 5 minutes. After addition of ethyl-β-chloropropionate (68 g.; 1 mol.) and refluxing for 8 hours the liquid was filtered from sodium chloride, the solvents removed, and the product hydrolysed as before, concentrated hydrochloric acid (600 c.c.) and water (300 c.c.) being used. The yield of faintly coloured acid was 77·5 g., m. p. 175—177°. Method (a) yields 80 g. of the acid from 53 g. of benzaldehyde.

The *trimethyl* ester (VIII; R = Me) was prepared by refluxing the acid (70 g.) with absolute methyl alcohol (400 c.c.) containing hydrogen chloride (16 g.) for 18 hours, removing the alcohol and water under diminished pressure, distilling twice with benzene (100 c.c.), and refluxing as before with methyl-alcoholic hydrogen chloride (200 c.c.). After working up in the usual way the ester was obtained as a colourless oil, b. p. 182°/0·15 mm. (yield 69·6 g.) (Found: C, 62·1; H, 6·6. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·6%). This ester slowly crystallised, giving after several days a solid mass, m. p. 50—56°. It was recrystallised from a large volume of light petroleum (b. p. 60—80°), giving small, flat prisms, m. p. 84—88° (Found: 62·4; H, 6·6%), undoubtedly a mixture of stereoisomers.

2-Phenylcyclopentan-3-one-1-carboxylic Acid (IX) *and Enolic Form* of *Dimethyl 2-Phenylcyclopentanone-3 : 5-dicarboxylate.*—The preceding trimethyl ester (61·6 g.) was added to a solution of anhydrous sodium methoxide (21·6 g.) in absolute methyl alcohol (160 c.c.), and the mixture refluxed for 3½ hours. The methyl alcohol was now removed under diminished pressure and the residual oil (*) hydrolysed by refluxing it for 16 hours with concentrated hydrochloric acid (500 c.c.) and water (250 c.c.). A little charcoal was then added, and the boiling mixture filtered rapidly through a sintered glass funnel. The 2-phenylcyclopentan-3-one-1-carboxylic acid (IX) separated in fine prisms, m. p. 115° with some previous softening (Chatterjee, *loc. cit.*, gives m. p. 114—115°) (yield 37 g.).

When the cyclisation product obtained in the preceding reaction (*) was shaken in ethereal solution with aqueous sodium hydrogen carbonate, there was extracted a weakly acidic product (5—10 g.) which crystallised from dilute alcohol in flat, almost rectangular plates, m. p. 152° (Found: C, 65·0; H, 5·6. $C_{18}H_{16}O_5$ requires C, 65·1; H, 5·8%). This compound gives a powerful violet ferric chloride reaction in dilute alcohol, and is probably an *enolic form* of dimethyl 2-phenylcyclopentanone 3 : 5-dicarboxylate. The intensity of the ferric chloride reaction suggests that it is the hydrogen atom attached to carbon atom 5 of the cyclopentanone nucleus which is involved in the enolisation. Hydrolysis with hydrochloric acid as described above gives 2-phenylcyclopentan-3-one-1-carboxylic acid.

Reduction of 2-Phenylcyclopentan-3-one-1-carboxylic Acid (IX) *to 2-Phenylcyclopentane-1-carboxylic Acid* (IV).—As the Clemmensen reduction carried out by Chatterjee (*loc. cit.*) led to an impure liquid acid, the following details of our procedure are given.

The keto-acid (IX) (18·3 g.), amalgamated zinc (200 g.), water (200 c.c.), concentrated hydrochloric acid (200 c.c.), and toluene (100 c.c.) were refluxed for 40 hours, with the addition of hydrochloric acid (50 c.c.) after 20 and 30 hours. The diluted liquid was extracted with ether; the extracts yielded a non-acidic oil (0·7 g.) and a mainly solid acid which, after crystallisation from light petroleum (b. p. 60—80°), gave the acid (IV), m. p. 87—88° (8·8 g.) (Found: C, 75·5; H, 7·4), identical (mixed m. p.) with that previously prepared by the condensation of benzene with cyclopent-1-enecarboxylic acid.

3-Phenylcyclopentyldimethylcarbinol (X).—Methyl 3-phenylcyclopentane-1-carboxylate was prepared from the acid (VI) by the Fischer–Speier method as an oil, b. p. 159—160°/20 mm.; $n_D^{18°}$ 1·524. The ester (6·3 g.) in dry ether was added to the Grignard reagent prepared from magnesium (1·5 g.), methyl iodide (8·8 g.), and ether (50 c.c.), and after 12 hours the ether-soluble material was refluxed for ½ hour in aqueous-alcoholic sodium hydroxide to hydrolyse any unchanged ester, and the neutral *carbinol* isolated and distilled (4·6 g.); b. p. 176°/24 mm.; $n_D^{18°}$ 1·5348 (Found: C, 81·8; H, 9·6. $C_{14}H_{20}O$ requires C, 82·3; H, 9·8%).

3-Phenylcyclopentanone (XI) *and Derivatives.*—The carbinol (X) (3 g.) in acetic acid (15 c.c.) was treated at *ca.* 35° with a solution of chromic acid (1·5 g.) in water (3 c.c.) and acetic acid (15 c.c.). After 24 hours the green solution was diluted and extracted with ether, the extracts shaken with water and aqueous sodium carbonate, dried, and the solvent removed, leaving crude 3-phenylcyclopentanone as a pleasant-smelling oil. This was characterised, and the position of the carbonyl group established, by the

preparation of the dibenzylidene derivative (XII; R = Ph), m. p. 181° (Borsche and Menz, *Ber.*, 1908, **41**, 204, record m. p. 181°), and the *dipiperonylidene* derivative (XII; R = 3 : 4-methylenedioxyphenyl). The latter separated when an alcoholic solution of the crude ketone was treated with excess of piperonal and a drop of concentrated aqueous potassium hydroxide. After two crystallisations from ethyl acetate it formed bright-yellow, square-ended needles, m.p. 220° (Found: C, 76·7; H, 4·9. $C_{27}H_{20}O_5$ requires C, 76·4; H, 4·8%).

4-*Keto*-1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII).—The liquid 3-phenyl*cyclo*pentane-1-carboxylic acid (VI) (5 g.) was added to a cooled mixture of phosphoric acid (25 c.c.; *d* 1·75) and phosphoric anhydride (25 g.), well stirred, and then heated on the steam-bath for 3 hours, water added, and the crude ketone extracted with ether. The extracts from 9 such experiments were united, washed with 15% aqueous sodium hydroxide (yield of recovered distilled acid, 4·2 g.), then with water, dried, and distilled twice, giving 4-*keto*-1 : 3-endo*ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII) (30·7 g., yield 85% allowing for the recovered acid) as a colourless oil, b. p. 162—163°/23 mm.; $d_{4^\circ}^{25^\circ}$ 1·119; $n_D^{25^\circ}$ 1·577 (Found: C, 83·5; H, 7·4. $C_{13}H_{12}O$ requires C, 83·7; H, 7·0%). The 2 : 4-*dinitrophenylhydrazone* was crystallised from dioxan and then from a mixture of chloroform and ethyl acetate, and obtained as dark red needles, m. p. 248—249° (Found: C, 61·1; H, 4·4; N, 16·2. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·5; N, 15·9%). This derivative is most conveniently crystallised from glacial acetic acid, but the melting point is then slightly lower, 244—246°, owing to retention of a trace of acetic acid. The *semicarbazone* prepared from the ketone (VII) (1 g.), alcohol (4 c.c.), water (3 c.c.), semicarbazide hydrochloride (1 g.), and hydrated sodium acetate (1 g.) at 30° for 1 hour and left overnight, was collected and washed with 50% alcohol (yield 1·25 g.). It separates from methyl alcohol in thick prisms which melt at *ca.* 170—171° with loss of solvent, resolidify, and finally melt at 191° (Found in material dried at 80° in a vacuum: C, 66·3; H, 6·8; loss of methyl alcohol on heating to 160°, 5·4. $C_{13}H_{15}ON_3,\frac{1}{4}MeOH$ requires C, 66·1; H, 6·6; MeOH, 6·5%). From ethyl alcohol, the stout rhombic prisms melt at *ca.* 167—169° with loss of solvent (Found: loss in weight at 160°, 7·8. $C_{13}H_{15}ON_3,\frac{1}{4}EtOH$ requires loss, 9·1%). From toluene, the white elongated prisms partially melt at 120—130°, then resolidify, and melt again at 191° [Found in material heated at 145° in a vacuum for 1 hour: N, 18·3. $C_{13}H_{15}ON_3$ requires N, 18·3%. Loss of toluene between 100° and 145° (no loss below 100°) in a vacuum, 16·8. $C_{13}H_{15}ON_3,\frac{1}{2}C_7H_8$ requires loss, 16·7%]. The toluene of crystallisation is readily detected by a micro-modification of Ramsden's test for aromatic hydrocarbons (see Bradley, Robinson, and Schwarzenbach, *J.*, 1930, 812). A few mg. of the substance are gently heated in a small ignition tube loosely fitted with a cork carrying a thin glass rod, the end of which has been dipped in a solution of paraformaldehyde in concentrated sulphuric acid, reaching to within about ½ inch of the bottom of the tube. The rapid appearance of a pinkish-brown colouration on the glass rod indicates the presence of the vapour of the aromatic hydrocarbon.

4-*Keto*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*cyclo*pentindene* (III).—2-Phenyl*cyclo*pentane-1-carboxylic acid (IV) (3 g.; m. p. 86—87°) was cyclised as in the previous case. The *ketone* (2 g.) was isolated as an oil, b. p. 152°/17 mm.; $d_{18^\circ}^{18^\circ}$ 1·101; $n_D^{20^\circ}$ 1·5742 (Found: C, 84·0; H, 7·1. $C_{13}H_{12}O$ requires C, 83·7; H, 7·0%). The 2 : 4-*dinitrophenylhydrazone*, after two crystallisations from glacial acetic acid, formed dark-red needles, m. p. 216—217° (Found in material dried at 100° in a vacuum over potassium hydroxide: C, 61·2; H, 4·3; N, 15·9. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·5; N, 15·9%). The *semicarbazone*, prepared as in the case of the isomeride (VII), was twice crystallised from a large volume of ethyl alcohol, and formed elongated, hexagonal plates, m. p. *ca.* 242° (decomp.; rapid heating) (Found: C, 68·3; H, 7·0; N, 18·5. $C_{15}H_{15}ON_3$ requires C, 68·1; H, 6·6; N, 18·3%).

1 : 3-endo*Ethylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII).—The ketone (VII) (1 g.), amalgamated zinc (10 g.), and concentrated hydrochloric acid (50 c.c.) were refluxed for 3 hours, dilute hydrochloric acid (50 c.c.) added, and heating continued for a further 8 hours. The diluted mixture yielded to ether a volatile mobile oil (410 mg.), b. p. 115—130°/20 mm. Fractionation gave the *hydrocarbon* (XIII), b. p. 117°/25 mm. (Found: C, 91·1; H, 9·1. $C_{12}H_{14}$ requires C, 91·1; H, 8·9%).

A *monosulphonamido*-derivative of (XIII) was prepared as follows. Chlorosulphonic acid (5 c.c.) was added during 5 minutes to a stirred solution of the hydrocarbon (1 g.) in chloroform (10 c.c.) at 0°. Stirring was continued for 1 hour, ice added, and the dried chloroform layer distilled and the residue treated with powdered ammonium carbonate for ½ hour at 100°. The product, isolated by the addition of water and purified by solution in aqueous sodium hydroxide, separated from benzene in plates (430 mg.), m. p. 133—145°. Repeated crystallisation from benzene raised the m. p. to 151—156° (Found: C, 61·0; H, 6·3; N, 6·2; S, 13·6. $C_{12}H_{15}O_2NS$ requires C, 60·8; H, 6·3; N, 5·9; S, 13·5%).

Ethyl 1-*Benzyl*cyclo*pentan*-2-*one*-1-*carboxylate*.—To sodium (7·6 g.) powdered under toluene was added a solution of ethyl *cyclo*pentan-2-one-1-carboxylate (52 g.) in benzene (250 c.c.), and the formation of the sodio-derivative completed by heating on the steam-bath for 2½ hours. Benzyl chloride (60 c.c., 1·5 mols.) was then added; the mixture was heated on the steam-bath for 14 hours, and, after the addition of water, the benzene layer was separated, the aqueous layer extracted with ether, and the two organic layers united, dried (Na_2SO_4), and distilled. The ethyl 1-benzyl*cyclo*pentan-2-one-1-carboxylate was obtained as a colourless oil (60 g., 73% yield), b. p. 183—186°/20 mm. (Found: C, 73·2; H, 7·4. Calc. for $C_{15}H_{18}O_3$: C, 73·2; H, 7·3%).

2-*Benzyl*cyclo*pentan*-1-*one* (XIV).—Ethyl 1-benzyl*cyclo*pentan-2-one-1-carboxylate (60 g.) and concentrated hydrochloric acid (200 c.c.) were refluxed for 18 hours, with the addition of a further quantity of acid (100 c.c.) after 7 hours. Dilution, extraction with ether, and distillation gave 2-benzyl-*cyclo*pentanone (28 g.), b. p. 150—155°/18 mm., $n_D^{17^\circ}$ 1·534, and a fraction, b. p. 155—190°/18 mm., consisting largely of unhydrolysed ester, which after hydrolysis as before yielded a further quantity of 2-benzyl*cyclo*pentan-1-one (6·8 g., b. p. 153—154°/19 mm.; $n_D^{17^\circ}$ 1·534; $d_{4^\circ}^{20^\circ}$ 1·038). The semicarbazone separated from methyl alcohol in plates, m. p. 198—200° (Duff and Ingold, *loc. cit.*, record the same m. p.).

1 : 3-*Diketo*-2-*acetonylindane*.—A solution of 1 : 3-diketoindane (4·9 g.; Teeters and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 3026) in ethyl alcohol (20 c.c.), ethyl acetate (60 c.c.), and chloroacetone (3·1 g.) was added during 45 minutes to a stirred solution of sodium (0·8 g.) in alcohol (40 c.c.) at 0°. Five minutes

after the addition the product was filtered from sodium chloride, and the filtrate acidified with a few drops of acetic acid and evaporated to dryness under diminished pressure on the water-bath. The dark residue was triturated with ether (500 c.c.) in 10 portions, and the ethereal solutions filtered and distilled to a small volume (10 c.c.); on standing, a crystalline material separated. This was crystallised several times from light petroleum (b. p. 80—100°), giving finally colourless needles (120 mg.), m. p. 129—130° (Found: C, 71·1; H, 5·0. $C_{12}H_{10}O_3$ requires C, 71·3; H, 4·9%).

Indan-3-one-1-carboxylic Acid (XV).—Phenylsuccinic acid (40 g.; Baker and Lapworth, *Org. Synth.*, Coll. Vol. I, p. 451) and thionyl chloride (40 c.c.) were heated on the water-bath for ½ hour. Dry nitrobenzene (80 c.c.) and anhydrous aluminium chloride (40 g.) were added, the mixture kept at 80° for 1½ hours, then poured into water (1 l.) and boiled to expel all nitrobenzene, water (250 c.c.) being added during the distillation so that the final volume was 700 c.c. The boiling solution, after addition of charcoal (20 g.), was filtered and cooled rapidly with shaking. The colourless, crystalline acid was collected, washed, and dried on the steam-bath till the melt of the hydrated acid (m. p. 84°) solidified to the anhydrous acid, m. p. 120°. Yield, 16·0 g. From the filtrate two further crops of the acid were obtained (4·4 g. and 2·0 g.; total 22·4 g., 61%) (Found in material crystallised from benzene: C, 68·1; H, 4·8. Calc. for $C_{10}H_8O_3$: C, 68·1; H, 4·6%).

The *ethyl* ester, prepared in the usual way, formed an oil, b. p. 198°/37 mm., which solidified, and, after crystallisation from warm light petroleum (b. p. 40—60°), was obtained in thin, nacreous, rectangular plates, m. p. 49—50° (Found: C, 70·5; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The *semicarbazone* of this ethyl ester formed small crystals from alcohol, m. p. 207—209° (decomp.) (Found: C, 59·9; H, 5·7. $C_{13}H_{15}O_3N_3$ requires C, 59·8; H, 5·8%).

Difficulty was experienced in preparing the amide from the foregoing ester owing to the formation of dark, intractable products. The ester (0·5 g.) was mixed with aqueous ammonia (10 c.c.; *d* 0·88) and just enough alcohol to give a homogeneous solution. After standing overnight the dark brown solution was evaporated to dryness, and the amide crystallised thrice from water (charcoal), giving colourless needles (0·1 g.), m. p. 177—178° (Found: C, 68·8; H, 5·4; N, 8·3. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%).

Condensation of Ethyl Indan-3-one-1-carboxylate with Ethyl Acetate.—To a solution of sodium (0·6 g.; 2 mols.) in ethyl alcohol was added ethyl acetate (30 c.c.), and then, in an atmosphere of nitrogen, a solution of ethyl indan-3-one-1-carboxylate (3 g.) in ethyl acetate (15 c.c.). The dark reddish-brown mixture was kept for 48 hours (in contact with air it became bright green). Excess of 2N-sodium hydroxide was added, and the mixture was extracted with ether, acidified, and the reddish product taken up in ether and shaken with aqueous sodium hydrogen carbonate. The ether yielded an oil which partly crystallised on treatment with methyl alcohol, and, after being pressed on porous porcelain, was finally obtained from light petroleum (b. p. 60—80°) (charcoal) as faintly purple, hexagonal plates (0·1 g.), m. p. 85—86° (Found: C, 68·3; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). This *compound*, either ethyl 2-acetylindan-3-one-1-carboxylate, or ethyl β-keto-β-(3-keto-1-indanyl)propionate, gives a deep red colour with alcoholic ferric chloride.

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188. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part XIII.* αβ-*Unsaturated Ketones and Quinones.*

By H. P. ROTHBAUM, I. TING, and P. W. ROBERTSON.

The velocities of chlorine addition in the presence of sodium acetate (electrophilic rate), and of bromine addition with different amounts of added sulphuric acid (nucleophilic rate), to benzylideneacetophenone and its *p*-methyl and *m*-nitro-derivatives have been measured in acetic acid solution. The theoretical interpretation of these results is discussed. Whereas a 1 : 4-diketone, such as Ph·CO·CPh:CH·COPh, shows very low electrophilic and nucleophilic rates, quinones by the acid-catalysed mechanism add one molecule of bromine very rapidly, and the second molecule with extreme slowness. This is in accord with the previous finding that a nucleophilic process which involves a structure with adjacent positive polarities has a low rate for bromine addition (cf. Part IX, *J.*, 1945, 892).

THE kinetics of halogen addition to αβ-unsaturated ketones have hitherto been little investigated. Ralls (*J. Amer. Chem. Soc.*, 1940, **62**, 3485) has measured the rates of bromine addition, in the presence of an equivalent amount of iodine, to CHPh:CH·CO·C_6H_4Br(*p*) in acetic acid and carbon tetrachloride solution. A novel instance of steric hindrance is shown by the oxime of this ketone, the *cis*-stereoisomer adding bromine at a slower rate than the *trans*-compound.

Part VIII of this series (*J.*, 1945, 888) deals with the kinetics of chlorine and bromine addition to αβ-unsaturated aldehydes. These compounds in acetic acid solution show acid-catalysed nucleophilic halogen addition; the reactions are insensitive to light, the rates

are reduced by adding water to the solvent, and bromine addition is in general more rapid than chlorine addition. With regard to constitutional effects, the influence of substituents is usually in the reverse order to that found for electrophilic reactions. An investigation of halogen addition to the related ketones, CHR:CH·COR′, is possible when R′ is a radical such as phenyl or *tert.*-butyl, which does not permit halogen replacement. The present investigation deals chiefly with the kinetics of chlorine and bromine addition to benzylideneacetophenone, and its derivatives with a substituent in one of the phenyl groups. As relative to the rate of bromine addition the electrophilic rate for chlorine is high, and the nucleophilic rate is low, the velocity of chlorine addition (in the presence of sodium acetate to eliminate any acid-catalysed nucleophilic addition) is a measure of the electrophilic reaction, whilst bromine addition in the presence of acid proceeds by the nucleophilic mechanism. In the following table, such electrophilic and nucleophilic rates are shown for CHPh:CH·COPh and certain related compounds. The measurements were made in acetic acid solution at 24°, reactants M/80.

Compound.	CHPh:CH·CHO.	CHPh:CH·COPh.	CHPh:CH·CO_2Et.
k_2 (Cl_2, M/80-NaOAc)	1·8	61	10·0
k_2 (Br_2, M/80-H_2SO_4)	27	32	0·013 *

* Corrected by subtraction of electrophilic rate.

It will be noted that benzylideneacetophenone adds chlorine more rapidly than ethyl cinnamate, despite the fact that, as far can be judged from nucleophilic reactivity, the benzoyl group is more strongly electron-attracting than the carbethoxy-group. A similar difference is found for the corresponding *m*-nitro-compounds, the rates for chlorine addition in acetic acid at 24° being: *m*-NO_2·C_6H_4·CH:CH·COPh, $k_2 = 0{\cdot}23$; *m*-NO_2·C_6H_4·CH:CH·CO_2Et, $k_2 = 0{\cdot}011$. Thus the importance of polarizability influences in halogen addition, as envisaged by Ingold and Ingold (*J.*, 1931, 2354), is again exemplified. When electrophilic reactivity is required by the reagent, the phenyl group (in benzoyl) appears to be more polarizable than the ethoxy-group (in carbethoxy-), as is shown also by the rates of second-order chlorination of *p*-RO·C_6H_4X, where for X = COPh and CO_2Et, the relative rates are 287 and 189 respectively (Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 743).

With reference to the nucleophilic reactions, both cinnamaldehyde and benzylideneacetophenone should add bromine at a considerably faster rate than ethyl cinnamate (as is experimentally found), since aldehydes and ketones have the normal nucleophilic reactivity, which esters do not possess. But whereas an aldehyde such as R·CHO is more highly reactive than a ketone, R·COPh, the rates of nucleophilic bromine addition to the cinnamaldehyde and benzylideneacetophenone do not differ greatly. Similarly, the rates with HBr_3, although too rapid for accurate measurement, are approximately the same [k_2 ($\frac{1}{4}$ mol. HBr), *ca.* 300]. A dual effect is here in operation. The replacement of the aldehyde hydrogen by phenyl increases the basicity, aiding the first stage of the acid-catalysed reaction, but the benzoyl group has a smaller electron-attracting power than the aldehyde group, and this is unfavourable to the second stage, which involves a nucleophilic attack on the positive β-carbon atom of the system.

The rates of electrophilic chlorine addition to compounds of the types C_6H_4X·CH:CH·COPh and CHPh:CH·CO·C_6H_4X are given in the following table, the measurements being made in acetic acid at 24°, reactants M/80, sodium acetate M/40.

(I) Ph·CH:CH·COPh	$k_2 = 61$	(V) *m*-NO_2·C_6H_4·CH:CH·COPh	$k_2 = 0{\cdot}23$
(II) Ph·CH:CH·CO·C_6H_4Me(*p*)	$k_2 = 61$	(VI) *p*-ClC_6H_4·CH:CH·COPh	$k_2 = 23$
(III) Ph·CH:CH·CO·C_6H_4·NO_2(*m*)	$k_2 = 15$	(VII) *p*-ClC_6H_4·CH:CH·CO·CMe_3	$k_2 = 36$
(IV) *p*-MeC_6H_4·CH:CH·COPh	$k_2 = ca.$ 800		

The effect of substituents in the benzoyl group is not large. The powerfully electron-demanding nitro-group reduces the rate, but only by a factor of 4 (III); a methyl group appears to have no effect on the rate (II). On the other hand, the influence of substituents in the second phenyl group (IV and V) is considerable, the methyl group increasing and the nitro-group reducing the rate. Such a difference may be partly attributable to the fact that electron-donor groups activate the β-carbon atom of the ethylenic system; in the above compounds, attack of halogen is α to the COR′ group, and therefore substituents in R (of R·CH:CH·COR′) will have a greater influence on the rates of addition than substituents in R′.

The following table gives the relative rates of chlorine addition for the substituted ketones examined in this paper and the corresponding cinnamic acids examined in Part IX (*J.*, 1945, 891).

	X = *p*-Me.	H.	*m*-NO_2.
C_6H_4X·CH:CH·COPh	13	1	0·0038
C_6H_4X·CH:CH·CO_2H.....	16	1	0·0017

With X = Cl (VI) there is in operation the normal dual effect, this substituent aiding the electrophilic mechanism by a tautomeric shift and acting reversely by induction. In general, the second effect tends to predominate in reactions that require a flow of electrons to the point of attack, and in this series of compounds the *p*-chloro-derivative reacts at about one-third of the rate of the unsubstituted compound.

Compounds (VI) and (VII) permit a comparison of the influence of the benzoyl and the pivaloyl group in determining the electrophilic rate. As ketones of the type R·CO·CMe_3 are considerably more reactive than R·CO·Ph, the relative rates of chlorine addition should therefore be (VII) > (VI). This is the experimental order, although a greater difference in reactivity was to be expected, if the electron-attracting power of the group COR′ was the sole determining factor.

The next table gives the rates of bromine addition (as bimolecular coefficients) to the substituted benzylideneacetophenones under various conditions, the measurements being made in acetic acid at 24° reactants M/80.

	NaOAc, M/40.	No catalyst.	H_2SO_4, M/40.	H_2SO_4, M/10.	H_2SO_4, M/5.
(I) Ph·CH:CH·COPh	0·33 *	15	35	47	50
(II) Ph·CH:CH·CO·C_6H_4Me(*p*)	0·33	16	29	29	—
(III) Ph·CH:CH·CO·C_6H_4·NO_2(*m*)	0·22	4	13	22	28
(IV) *p*-MeC_6H_4·CH:CH·COPh	7·8	64	73	73	—
(V) *m*-NO_2·C_6H_4·CH:CH·COPh	0·09	7	40	53	61

* NaOAc, M/160, $k_2 = 0·31$.

The influence of the base sodium acetate in the acid solvent is to eliminate the acid-catalysed nucleophilic reaction, so that the rates in the first column should be those of electrophilic bromine addition. The value for compound (V), however, is too high, as judged by the corresponding rates for electrophilic chlorine addition; it is possible therefore that acetic acid molecules, as well as hydrogen ions, may be effective to a slight extent in the nucleophilic reaction. A change in the sodium acetate concentration, examined for (I) (cf. table), has little influence on the rate of bromine addition. When sodium acetate is present, there is considerable sodium bromide formation, with the result that at lower concentrations of sodium acetate there is a sudden increase in rate (reactants M/80, sodium acetate M/320, at *ca.* 40% bromine absorption) owing to the change-over to the rapid acid-catalysed reaction. Lithium chloride is also a base in acetic acid solution, and likewise depresses the rate of bromine addition; *e.g.*, for (I), reactants M/80, k_2 (LiCl, 0·027M), 3·1; k_2 (LiCl, 0·081M), 3·6. These values are higher than those found in the presence of sodium acetate, in part because lithium chloride is a weaker base, and in part because it acts as a catalyst for the reaction.

The acid-catalysed reactions are considered to proceed according to the scheme (Part VIII, *loc. cit.*):

$$A + H^{\oplus} \underset{2}{\overset{1}{\rightleftarrows}} AH^{\oplus};\ AH^{\oplus} + Br_2 \underset{4}{\overset{3}{\rightleftarrows}} A,Br_2 + H^{\oplus};\ A,Br_2 \xrightarrow{5} ABrBr.$$

When the maximum rate with added acid is reached, $-d[Br_2]/dt = k_1k_3k_5[A][Br_2]/k_2k_4$.

Reference to the table reveals that the influence of sulphuric acid in increasing the rate is relatively greater for the weaker bases (III and V) than for the stronger bases (II and IV), for which the maximum rate is reached at a lower concentration of added acid. Benzylideneacetophenone (I) in this respect occupies an intermediate position, but, being a stronger base than cinnamaldehyde (Part VIII, *loc. cit.*), it shows a maximum rate with a lower concentration of acid. For the same reason the rates of (I) with perchloric acid (a stronger acid than sulphuric acid in acetic acid solution) are only slightly greater than with sulphuric acid (M/40-$HClO_4$, $k_2 = 42$; M/10-$HClO_4$, $k_2 = 48$), whereas for cinnamaldehyde the differences were greater.

With regard to the influence of substitutents in the phenyl groups of benzylideneacetophenone on the nucleophilic rates, our previous comparison of this compound and cinnamaldehyde has indicated that large differences were not necessarily to be expected for this kind of reaction. Here, similarly, dual opposing electronic effects are in operation, and, moreover, the extent of the acid catalysis varies from compound to compound, so that a choice of comparable conditions is involved. A further complication is that the reactions appear to be autocatalytic (see Experimental).

The rate of bromine addition to a 1 : 4-diketone, Ph·CO·CPh:CH·COPh, has also been measured in acetic acid at 24°, reactants M/80:

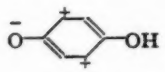
$$k_2\ (M/40\text{-NaOAc}) < 0·0005;\ k_2\ (M/40\text{-}H_2SO_4) = 0·048;\ k_2\ (M/10\text{-}H_2SO_4) = 0·090$$

The very low electrophilic rate (in presence of sodium acetate) is due to the electron-abstraction by the two carbonyl groups. In the acid-catalysed nucleophilic reaction a low rate, *i.e.*, relative to that of benzylideneacetophenone, is to be expected, since the formation of the positive ion may set up an unfavourable structure with adjacent positive polarities, *viz.*, $\overset{-}{O}\cdot\overset{+}{C}Ph\cdot\overset{+}{C}Ph\cdot CH{:}CPh\cdot OH$ (cf. Part IX, *loc. cit.*).

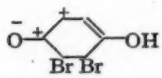
The *p*-benzoquinones, which have a similar unsaturated system, show likewise a low electrophilic rate of bromine addition, but on the other hand are characterised by very rapid acid-catalysed bromine addition in acetic acid solution. Thus the following values were obtained for thymoquinone in acetic acid at 24°, reactants M/80 :

$$k_2\ (\text{M}/40\text{-NaOAc}) < 0{\cdot}01;\ k_2(\text{M}/80\text{-}H_2SO_4) \sim 100$$

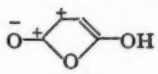
In a quinone, the formation of a positive ion can take place to give a structure (VIII) without the necessity of adjacent polarities, so that a high nucleophilic reactivity may be predicted. But even more reactive than the univalent ion could be the bivalent ion [formed from (VIII)] with its double positive charge, and it is possibly due to ions of this kind that quinones generally add bromine at such a high nucleophilic rate.



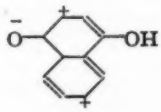
(VIII.)



(IX.)



(X.)



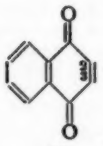
(XI.)

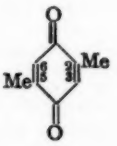
When one molecule of bromine has been added to thymoquinone in acetic acid solution the reaction comes virtually to a stop, even in the presence of sulphuric acid, further absorption of bromine taking place with extreme slowness ($k_2 < 0{\cdot}0005$). This is in accord with theoretical expectation; in the dibromo-addition product of a quinone, part of the tautomeric system is blocked, and in the positive ion (IX) conditions are possible for adjacent polarities. At the same time the bromine atoms by their inductive effect tend to weaken the compound as a base and prevent salt formation, thus tending still further to reduce the nucleophilic rate of bromine addition. Similarly, maleic anhydride, which has a structure also leading to formation of adjacent polarities (X), adds bromine by the nucleophilic mechanism relatively slowly, and at the same time is characterised, owing to the considerable regression from the ethylenic system, by a very low electrophilic rate, as seen from the velocities in acetic acid at 24°, reactants M/80 :

$$k_2\ (\text{M}/40\text{-NaOAc}) < 0{\cdot}0005;\ k_2\ (\text{M}/160\text{-}H_2SO_4) = 0{\cdot}0036;\ k_2\ (\text{M}/10\text{-}H_2SO_4) = 0{\cdot}0082$$

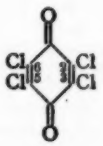
Bromine addition to certain quinones has been measured in 1% aqueous acetic acid, in which solvent the rates of acid-catalysed addition are less than in acetic acid and become more conveniently measurable. The following relative velocities have been found, reactants M/80 + M/160-sulphuric acid :

100.


40.



3.



0.

In naphthaquinone the tautomeric system is not blocked, as is indicated by the formulation of one of the resonance structures of its ion (XI, above). Since positive-ion formation for naphthaquinone involves a greater change in the number of possible resonance structures than for benzoquinone, it can be assumed to be a weaker base, and for this reason its nucleophilic reactivity should be less. With OH in the 1 position, there is one point of nucleophilic attack (3) for naphthaquinone, but for benzoquinone two such points of attack (3 and 5); moreover, the fused benzene ring in the molecule should exert no polar influence on the 3-position. The rate for naphthaquinone should therefore be expected to be less than half that of benzoquinone.

The nucleophilic constitutional effects, *i.e.*, the reversal of the electrophilic order, observed for αβ-unsaturated acids (Part V) and for certain αβ-unsaturated aldehydes (Part VIII), but obscured in the αβ-unsaturated ketones (present communication), become again evident in the

case of *p*-xyloquinone. In this compound the methyl groups cause an electronic flow to the oxygen atoms, thereby aiding combination with hydrogen ions, the first stage of the reaction, but, at the same time, the methyl groups, by their inductive power, tend to neutralise the positive charges thus formed on the carbon atoms and so hinder the nucleophilic attack. This second effect predominates, and *p*-xyloquinone adds bromine by the nucleophilic mechanism more slowly than benzoquinone itself.

Tetrachlorobenzoquinone was found not to add bromine in acetic acid in the presence of sulphuric acid. As this compound reacts with hydroxyl ions to form chloranilic acid, partial positive charges are developed in the 2 : 5 (or 3 : 6) positions by resonance, but this in itself is not sufficient to cause nucleophilic bromine addition, which requires the actual formation of a positive ion. Tetrachlorobenzoquinone, however, by the inductive effect of its four chlorine atoms, becomes so weak a base that salt formation is virtually prevented, and it therefore cannot add bromine by the nucleophilic mechanism.

Experimental.

The benzylideneacetophenones used in this investigation were prepared from the corresponding derivatives of benzaldehyde and of acetophenone : Ph·CH:CH·COPh, m. p. 57°; *p*-MeC_6H_4·CH:CH·COPh, m. p. 95°; *m*-NO_2·C_6H_4·CH:CH·COPh, m. p. 143°; Ph·CH:CH·CO·C_6H_4Me(*p*), m. p. 74°; Ph·CH:CH·CO·C_6H_4·NO_2(*m*), m. p. 128°; *p*-ClC_6H_4·CH:CH·COPh, m. p. 113°; *p*-ClC_6H_4·CH:CH·CO·CMe_3, m. p. 84°; Ph·CO·CPh:CH·COPh, m. p. 129°. In addition were used : *p*-benzoquinone, m. p. 116°; *p*-xyloquinone, m. p. 124°; thymoquinone, m. p. 45°; 1 : 4-naphthaquinone, m. p. 124°.

The general technique was as described in Part VIII (*loc. cit.*), and here are the details of a typical rate measurement :

Ph·CH:COPh, M/80 + Br_2, M/80 + H_2SO_4, M/20 in HOAc, 24°.

(2 Ml. pipetted into 5% KI soln. and titrated with N/80-$Na_2S_2O_3$.)

Time (mins.)	0	0·50	0·88	1·15	1·50	2·25
Titre (ml.)	4·01	3·60	3·05	2·65	2·30	1·56
Time (mins.)	0	0·44	0·81	1·20	1·96	2·71
Titre (ml.)	3·90	3·51	3·00	2·51	1·77	1·28

The % change–time curve from these two sets of measurements gave the following series of bimolecular coefficients :

x	10	20	30	40	50	60
k_2	20	27	33	40	46	53

As the time intercepts for different initial concentrations indicated a bimolecular reaction, the rising values of k_2 suggest that the reaction is autocatalytic. With *m*-NO_2·C_6H_4·CH:CH·COPh, under similar conditions, the autocatalysis becomes relatively less :

x	10	20	30	40	50	60
k_2	37	42	48	54	61	65

It is possible that the autocatalysis is due to hydrobromic acid produced by a concomitant electrophilic bromination, which would be less for the nitro-compound. Tests at the end of such reactions by adding silver nitrate dissolved in warm acetic acid showed a faint turbidity, indicating a small formation of hydrobromic acid, but possibly sufficient to cause the effect observed, as hydrobromic acid is a strong catalyst of the reaction. A rate comparison for these two compounds under conditions where acid autocatalysis is largely eliminated, namely, reactants M/320, HBr M/320, in CCl_4, 16°, showed Ph·CH:CH·COPh, $k_2 = 7{\cdot}3$, and *m*-NO_2·C_6H_4·CH:CH·COPh, $k_2 = 6{\cdot}7$. This result confirms the conclusion previously reached that, for nucleophilic bromine addition to the benzylideneacetophenones, there is relatively little change in rate from compound to compound.

The bimolecular coefficients quoted in the text are for the rapid reactions at $x = 50\%$ bromine or chlorine absorption, for the slow reactions at $x = 10\%$, whilst in the very slow reactions, where the change was of the same order as the experimental error, the results are given as $k_2 < 0{\cdot}0005$. The measurements with the quinones were less well reproducible than with the ketones, as a back reaction with the dibromo-product and potassium iodide tended to make the end-point uncertain. The times for the measurements in 1% aqueous acetic acid, from which the relative rates in the last table were derived, were for $x = 50$, benzoquinone, $t = 1{\cdot}7$, $2{\cdot}2$; naphthaquinone, $t = 4{\cdot}5$, $4{\cdot}8$; xyloquinone, $t = 65$, 65.

Victoria University College, Wellington, New Zealand. [*Received, July 5th*, 1947.]

189. *An X-Ray and Thermal Examination of the Glycerides. Part IX. The Polymorphism of Simple Triglycerides.*

By Charles E. Clarkson and Thomas Malkin.

M. p. and *X*-ray data are given for the β′-form of simple triglycerides, which thus exist in four solid modifications and exhibit the same type of polymorphism as the mixed triglycerides discussed in Parts IV, V, VI, and VII (*J.*, 1939, 103, 577, 1141, 1518). The suggestion of Lutton (*J. Amer. Chem. Soc.*, 1945, **67**, 524) and Longenecker and Daubert (*Ann. Rev. Biochem.*, 1945, **14**, 126) that the concept of the glassy (vitreous) state of triglycerides should be eliminated is shown to be untenable.

In Part I (*J.*, 1934, 666) it was shown that simple triglycerides exist in three modifications, namely, the α, β, and vitreous forms; but on extending the study to mixed triglycerides (Parts IV to VII, *locc. cit.*) a fourth form, termed β′, was also observed. This led us to re-examine the simple triglycerides, and we found evidence for the β′-form for those containing odd membered acids (cf. Grüntzig, who reported our results, *Z. anorg. Chem.*, 1939, **240**, 313). At this stage our work was interrupted, but subsequently other workers have reported the expected β′-form for triglycerides containing even-membered acids (Bailey, Jefferson, Kreeger, and Bauer, *Oil and Soap*, 1945, **22**, 10; Lutton, *loc. cit.*; Filer, jun., Sidhu, Daubert, and Longenecker, *J. Amer. Chem. Soc.*, 1946, **68**, 167).

Although these workers obtained *X*-ray evidence for the β′-form, they did not observe any corresponding m. p., neither could they obtain the simple *X*-ray photograph given by the vitreous form. Consequently, Lutton, and Longnecker and Daubert, finding *X*-ray evidence for α, β′, and β forms only, and being aware of only three m. p.s, namely those reported by us for the vitreous, α, and β forms, concluded that we had erroneously associated the *X*-ray patterns and m. p.s. According to them, the three known m. p.s of simple triglycerides are those of the α, β′, and β forms, and the concept of the glassy (vitreous) state of triglycerides should be eliminated.

There are many objections to this view. In the first place, it postulates the existence of only three solid modifications for triglycerides, whereas in Parts IV—VII of this series four modifications have been indubitably established for some forty triglycerides. Again, if our α-m. p.s, which form a non-alternating series, were β′-m. p.s as suggested by Lutton, they would be expected to alternate, since β′-forms of triglycerides are known to possess tilted chains (cf. Malkin, *J.*, 1931, 2796). Moreover, Ravich, Zurinov, Volnova, and Petrov have recently adduced optical and other evidence for the vitreous form of simple triglycerides (*Acta Phytochim.*, 1946, **21**, 101).

Finally, we now report a fourth m. p. (β′) for simple triglycerides, and thus all the saturated triglycerides so far investigated by us exist in four solid modifications, namely, in order of ascending m. p., vitreous, α, β′, and β.

Lutton * states (*loc. cit.*, p. 525): "The conclusive proof of the correspondence of the α-*X*-ray pattern with the lowest melting form, is the experimental result that actual samples which gave the α-*X*-ray pattern also exhibited the lowest form m. p. when tested immediately after *X*-ray exposure".

This evidence, however, is far from conclusive, since both the vitreous and the α-forms give rise to the same side spacing (cf. Figs. 4, 5, Plate), and it is clearly impossible to say whether or not a specimen giving the α-form spacings contains any vitreous form. Indeed, because of the greater crystallinity of the α-form, a specimen preponderantly vitreous would give an *X*-ray photograph very little different from that of an α-form. Again, we have stated in Part I (p. 669) that a number of minute crystalline aggregates are dispersed throughout the vitreous form, and that the exact nature of a solidified glyceride depends very much on the rate of cooling. In our experience, the rods obtained by Lutton by cooling 1 mm. diameter capillaries of molten glyceride from 100° to 0° for "two seconds or longer", would certainly contain varying amounts of α-form. Solid glycerides are extremely bad conductors of heat, and it is difficult to cool the interior of a rod or layer of any appreciable thickness quickly enough to avoid some α-formation. Fig. 5, Plate, was obtained from as thin a layer as possible, cooled rapidly on a cover slip. A specimen treated as stated by Lutton would be expected to melt more or less completely at the vitreous m. p., except for a cloud of α-nuclei which would initiate rapid α-solidification, followed most probably by some α ⟶ β′ transition in the solid state.

Lutton's deductions concerning his beta prime (β′) forms, which gave the softening

* In the following discussion it will suffice to deal with the fuller results of Lutton.

points of our α-forms but the *X*-ray pattern of the β′-forms, are equally debatable, and for the same reason. The strongest lines given by the α- and the β′-forms are practically the same (4·19 and 4·22 respectively), and it is not easy to be certain from an *X*-ray photograph that a β′-form is free from α-form. Our repetition indicates that his β′-forms contained considerable amounts of α-form. Indeed, the fact that Lutton speaks of " softening points " rather than melting points, is itself significant, and confirms this. Thus, all the lower-melting forms are metastable, and transitions into higher-melting forms can take place in the solid state. It is only, therefore, when these transitions are exceptionally slow, *e.g.*, with unsymmetrical mixed triglycerides (Part V), that homogeneous metastable forms can be obtained. Such a form melts to a clear liquid, with all the appearance of a true melting point, and some time may elapse before solidification in the next higher-melting form begins. If, however, owing to transition in the solid state, seeds of the higher-melting form are already present, the lower form melts to a cloudy liquid, which quickly solidifies in the higher-melting form, and, depending on the amount of higher-melting form initially present, the process becomes a softening rather than a melting. In the extreme case, where solid transitions are rapid, and a lower-melting form is full of seeds of higher-melting form, even softening may not be observed, and the m. p. may escape observation. This is the case with simple triglycerides of even acids, and considerable patience and repetition is required to determine the β′-m. p., which is best done as follows. Melt the specimen in a capillary tube, solidify it in ice, and then place it in a bath one or two degrees above the m. p. of the vitreous form. Complete or nearly complete melting takes place, followed closely by resolidification in the α-form, but after some three to six minutes longer at this temperature, a further change takes place, denoted by a shrinking from the walls of the capillary. Before this change the specimen melts almost completely at the α-m. p., but, after the shrinking, the α-m. p. is passed without any change in appearance until the β′-m. p. is reached. At this point, softening and very rapid resolidification in the stable β-form takes place.

In contrast to the above, transitions of glycerides of odd acids are much slower, and little difficulty is experienced in determining their β′-m. p.s.

Table I gives our latest m. p. data for simple triglycerides.

TABLE I.

	β.	β′.	α.	Vitreous.
Tristearin	72·0°	70·0°	65·0°	54·5°
Trimargarin	64·0	62·5	61·0	50·0
Tripalmitin	65·5	63·5	56·0	45·0
Tripentadecylin	54·0	53·0	51·5	40·0
Trimyristin	57·0	54·5	46·5	33·0
Tritridecylin	44·0	42·5	41·0	25·0
Trilaurin	46·4	—	35·0	15·0
Triundecylin	30·5	29·0	26·5	1·0
Tridecylin	31·5	—	18·0	−15·0

β′-M. p.s could not be observed for trilaurin and tridecylin.

X-Ray Investigation.—β′-Forms were obtained as described above, and side and long spacings determined. Owing to the rapid transition β′ ⟶ β for triglycerides of even acids, the lines of both these forms are usually present on the same photograph (cf. Fig. 8, Plate) where the inner strong line is the strongest line of the β-spacing (4·6 A.), the remaining two strong lines being the β′-spacings of 4·22 and 3·8 A. (Lutton, *loc. cit.*, gives 4·18 and 3·78 A.). No difficulty is experienced, however, in obtaining homogeneous β′-forms of odd acid triglycerides, as these can be kept for some time just below the β′-m. p. without transition into the stable form. By what appears to be more than a coincidence, the significance of which still eludes us, the side spacings of tritridecylin, tripentadecylin, and trimargarin are identical with those of the β-forms of β-myristodilaurin, β-palmitodimyristin, and β-stearodipalmitin respectively, the total chain lengths in the respective pairs being the same (cf. Figs. 13, 12, 11, Plate, with Figs. 11, 12, 13 on Plate facing page p. 107, *J.*, 1939 *). Long spacings of β′-forms of odd acid triglycerides are, within 0·2 A., the same as those of the β-forms.

As indicated above, the American workers have been misled in interpreting their *X*-ray data, because of the difficulty of obtaining homogeneous metastable forms, and whilst, at first glance, their results appear to support their view, it is not difficult to show that this is untenable. If, *e.g.*, the lowest-melting form of tristearin (m. p. 54·5°) is in fact the α-form, it

* The value, 4·48 A., given there for β-stearodipalmitin should be corrected to 4·38.

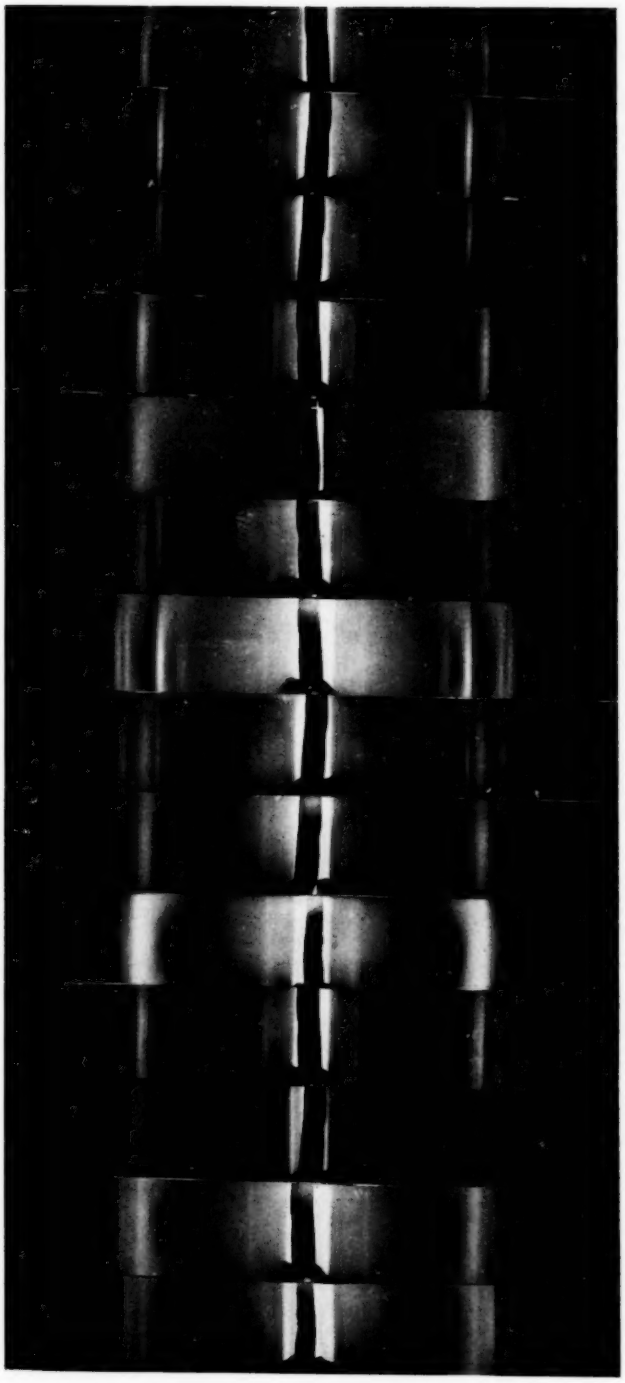


FIG. 1 — *Tristearin, mainly α, beginning to change to β.*

2 — *Tristearin, β.*

3 — ,, *α and β.*

4 — ,, *α.*

5 — ,, *vitreous.*

6 — ,, *α and β.*

7 — *Tripalmitin, β.*

8 — ,, *β′ and β.*

9 — ,, *α and β′.*

10 — *Trimargarin, α and β .*

11 — ,, *β′.*

12 — *Tripentadecylin, β′.*

13 — *Tritridecylin, β′.*

14 — *Triundecylin, β′.*

[*To face p.* 986

TABLE II.

Long and side spacings of β′-forms of simple triglycerides.

	Long.	Side.			
Tristearin	47·2	3·8	4·22		
Tripalmitin	42·6	,,	,,		
Trimyristin	37·6	,,	,,		
Trimargarin	43·7	3·79s	4·02w	4·19s	4·37w
Tripentadecylin	39·1	3·81s	4·12s	4·3s	
Tritridecylin	34·2	3·85m	4·04w	4·26s	4·43w
Triundecylin	29·5	3·88s	4·25s	4·52w	

	Lutton.			Bailey, *et alia*.		
Tristearin	46·8	3·78	4·18	46·4	3·79	4·19
Tripalmitin	42·3	,,	,,			
Trimyristin	37·65	,,	,,			

s = strong; m = moderate; w = weak.

should be impossible to obtain an *X*-ray photograph, showing the single side spacing of this form, at any temperature above 54·5°. Figs. 1 and 3 are photographs of a rod of tristearin, initially in the α-form, surrounded by an oven at a rising temperature from 57° to 64°. Fig. 1 shows the α-form at the top of the rod beginning to change to the stable β-form, whilst Fig. 3 (64°) shows the specimen mainly in the β-form, but still in the α-form in the lower part of the rod which is at a slightly lower temperature owing to contact with the metal spectrograph. (The curvature of the lines in this photograph is due to the fact that the specimen is now a shortened rod of β-form on top of a very short rod of α-form, instead of a uniform rod of normal length.) Again, Fig. 6 is a photograph of a rod of tristearin, originally α-form, after being in a thermostat at 60° for ½ hour. According to the American workers the α-form could not exist at this temperature, yet both α- and β-forms are present.

Repetition of Lutton's work leaves no doubt that his β′-forms contained varying amounts of α-form. A rod of tripalmitin made by his method for obtaining β′-forms, *i.e.*, melting the the specimen at 100°, cooling it in ice, and then keeping it at 45° for a minute or two, gave the photograph, Fig. 9, showing a strong diffuse inner line and a weaker sharper line. This is clearly a mixture of α- and β′-forms, the former predominating, since the true β′-form gives two lines of equal intensity (cf. Fig. 8). Moreover, by keeping the specimen for a longer period at 45°, or by increasing this temperature slightly, it is possible to increase the relative intensity of the weaker line, and the strong diffuse line becomes better defined as the α-line disappears. This is seen much more clearly with odd acid glycerides, where the β′-form gives a more definite and characteristic photograph uncomplicated by the $\beta' \longrightarrow \beta$ transition. By treating trimargarin according to Lutton's method for obtaining β′-forms one obtains Fig. 10, showing again the strong α-line overlaid by the weaker β′-lines, very similar, indeed, to the palmitin photograph. On raising the temperature of the specimen to just below the β′-m. p., the spacings of the β′-form alone are obtained (Fig. 11).

Our present results complete the broad picture of the polymorphism of saturated triglycerides. All that we have examined, whether simple or mixed, exist in four solid forms, *viz.*, vitreous, α, and β′ (crystalline, monotropic), and β (stable crystalline form). Except for those containing short chains (*i.e.*, C_{10}, C_{12}) rapid cooling (ice) brings about solidification mainly in the vitreous form, and this, on warming, undergoes the transitions $\alpha \longrightarrow \beta'$, $\beta' \longrightarrow \beta$, and also in some cases $\alpha \longrightarrow \beta$. These transitions are rapid for simple even acid, and symmetrical mixed triglycerides, and slow for simple odd acid, and unsymmetrical mixed triglycerides, the speed of transitions in all cases diminishing with increasing length of acid chain. Also, as would be expected, impurities decrease the rate of transitions. It is of interest to note that α-forms of simple even acid triglycerides may change directly into the stable β-form without passing through the intermediate β′-phase, and this may, of course, be true for other glycerides, although we have not observed it. The factors determining which transition takes place are not easy to determine, but in general $\alpha \longrightarrow \beta$ transition appears to be more probable the purer the glyceride and the smaller the amount of vitreous form present with the α-form on solidification.

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THE UNIVERSITY, BRISTOL. [*Received, July 7th*, 1947.]

190. *Lanosterol. Part V. Hydrogenation of the Inert Double Bond in Lanosterol Derivatives.*

By CHARLES DORÉE, J. F. MCGHIE, and FREDERICK KURZER.

The "inert" double bond of lanosterol, when situated between two carbonyl groupings, forming the chromophore —CO—C=C—CO—, can undergo reduction without difficulty. Diketodihydrolanosteryl acetate (Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, **27**, 472) and diketolanostene (see experimental part), for example, have been converted smoothly by several methods into the fully saturated compounds *diketolanostanyl acetate* and *diketolanostane* respectively. The substances are of interest in being the first lanosterol derivatives recorded in which the "inert" double bond of the ring system has been hydrogenated. Whether this inert linkage migrates during the oxidation of dihydrolanosteryl acetate to the diketo-derivative, and takes up a position more favourable to hydrogenation cannot, at present, be decided.

LANOSTEROL, a tetracyclic alcohol of triterpenoid character, contains two double bonds, one of which is reactive and readily hydrogenated, while the other is chemically inert. Reduction of the active unsaturated centre, situated in the terminal *iso*propylidene grouping of the side chain, yields dihydrolanosterol, which still contains the inert double bond. Agnosterol, with an identical carbon skeleton, differs from lanosterol only in the possession of a third double bond, also of the inert type. Our previous attempts to reduce the inert unsaturated linkage directly have so far been unsuccessful. Catalytic hydrogenation of dihydrolanosteryl acetate, using Raney nickel under pressures up to 150 atmospheres at 200°, and the action of hydriodic acid under severe conditions, have not produced a saturated derivative. A study of certain oxidation products of dihydrolanosterol and dihydroagnosterol, in which the inert linkage is still present, has shown, however, that in these cases the unsaturated centre can readily be reduced, giving derivatives corresponding to the, so far, unknown saturated hydrocarbon lanostane.

Dihydrolanosteryl acetate, when oxidised with chromium trioxide in glacial acetic acid, yields monoketo-, diketo-, and triketo-dihydrolanosteryl acetate (Marker *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, **27**, 472). The diketo-acetate, $C_{32}H_{50}O_4$, forms the main product of the reaction and is also produced by the oxidation of dihydroagnosteryl acetate (Ruzicka *et al.*, *loc. cit.*; Dorée and McGhie, *Nature*, 1944, **153**, 148). Diketodihydrolanosteryl acetate forms deep-yellow plates, and gives an absorption curve in the ultra-violet with a well defined maximum at $\lambda = 275$ mμ ($\log \varepsilon = 3{\cdot}94$), which suggests the presence of the chromophoric grouping —CO—C=C—CO—, the two carbonyl groups being formed by the oxidation of the methylene groups adjacent to the inert double bond. The displacement of the absorption maximum towards the longer wave-lengths of the spectrum in the case of monoketodihydrolanosteryl acetate ($\lambda_{max} = 255$ mμ) indicates, in accordance with Woodward's rule (*J. Amer. Chem. Soc.*, 1941, **63**, 1123), the location of the inert double bond between quaternary carbon atoms. The question whether the inert double bond is situated in the same position as in dihydrolanosteryl acetate, or has migrated to a new position during oxidation, cannot yet be decided.

In an attempt to reduce the ketonic groups of diketodihydrolanosterol and compare the reaction product with the original dihydrolanosterol, diketodihydrolanosteryl acetate was subjected to the Clemmensen reduction. The reaction, however, took an abnormal course, yielding saturated colourless *diketolanostanyl acetate*, $C_{32}H_{52}O_4$. This composition and the absence of the high-intensity maximum characteristic of the original chromophoric grouping suggested that hydrogenation of the ethenoid double bond of the chromophore system —CO—C=C—CO— had taken place, the "inert" unsaturated linkage being activated by the adjacent ketonic groups, so that reduction becomes possible. The abnormal course of the Clemmensen reduction was further apparent from the fact that diketodihydrolanosteryl acetate was reduced with equal facility by other reduction methods normally without effect on ketonic groupings. Thus, catalytic hydrogenation, using platinum oxide prepared according to Adams, and the action of zinc and acetic acid, gave high yields of diketolanostanyl acetate. Reduction with sodium and *iso*propyl alcohol gave, owing to simultaneous hydrolysis, diketolanostanol, $C_{30}H_{50}O_3$, the acetate of which was identical with the product obtained by the other methods. *Diketolanostanol* gives on oxidation the corresponding *diketolanostanone*. Owing to the absence of the chromophoric system, these saturated compounds are colourless and show no high-intensity absorption spectrum in the near-ultra-violet; diketolanostanyl acetate, for example,

produces only an absorption maximum, of very low intensity, at $\lambda = 298$ mμ. The keto-groups are unreactive and yield no dioxime or semicarbazone under the usual conditions.

Similar results were obtained with hydrocarbons of the lanosterol series. "α"-Lanostene ("dihydrolanostene"), $C_{30}H_{50}$, and agnostadiene ("γ"-lanostene), $C_{30}H_{48}$, corresponding to dihydrolanosterol and dihydroagnosterol, respectively, have been prepared by the Wolff–Kishner reduction of the ketone-semicarbazones (Ruzicka *et al.*, *loc. cit.*) and by direct reduction of the ketones (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467). Chromic acid oxidation of lanostene, under controlled conditions, gave a diketone, *diketolanostene*. The yellow colour of this, and the occurrence of the absorption maximum at $\lambda = 275$ mμ, indicate the presence of the same chromophore system as in diketodihydrolanosteryl acetate. Chromic acid oxidation of agnostadiene ("γ"-lanostene) also gave diketolanostene, identical with the product from "α"-lanostene. The production of the same oxidation product from both "α"-lanostene and agnostadiene recalls the behaviour of dihydrolanosterol and dihydroagnosterol, both of which are oxidised to the same diketo-derivative, and suggests the same distribution of the chromophore in the respective oxidation products. This view receives further support from the observation that, as in diketodihydrolanosterol, the double bond of the chromophore was readily reduced by the methods described above, yielding the saturated colourless *diketolanostane*.

The ease with which the double bond contained in analogous chromophores can be reduced has been recorded in related compounds. Wieland *et al.* (*Annalen*, 1939, **539**, 219, 242), for example, when oxidising the dimethylcarbinol of pyroquinovic acid, obtained a yellow diketone, $C_{30}H_{44}O_4$, showing maximum absorption at $\lambda = 270$ mμ, which was readily reduced with zinc and acetic acid to the saturated colourless compound $C_{30}H_{46}O_4$. Similarly, diketones with absorption maxima $\lambda = 273$—275 mμ, containing the chromophore —CO—C=C—CO, have also been obtained from "α" and "β"-elemolic acids by Ruzicka *et al.* (*Helv. Chim. Acta*, 1942, **25**, 1375, 1403): acetyldihydro-"α"-elemolic acid, for example, gave a yellow diketone, $C_{32}H_{48}O_6$ ($\lambda_{max} = 275$ mμ), which yielded colourless reduction products on catalytic hydrogenation.

The similarity between the behaviour of the oxidation products of lanosterol, quinovic acid, and the elemolic acids confirm the analogies already apparent between those compounds. Further reduction of diketolanostanol and diketolanostane should yield a series of saturated compounds corresponding to the unknown lanostane, and experiments in this direction are in progress.

Experimental.

Melting points are uncorrected. Optical rotations were determined in chloroform solution at 17°.

Diketodihydrolanosteryl Acetate.—This was prepared by Ruzicka's method (*Helv. Chim. Acta*, 1944, **27**, 472). Dihydrolanosteryl acetate (50 g.) dissolved in glacial acetic acid (1 l.), when oxidized with a solution of chromium trioxide (50 g.) in 90% acetic acid (250 ml.) for 3 hours, gave 60—70% yields of the diketo-compound, m. p. 157—158°; absorption maximum $\lambda = 275$ mμ ($\log \varepsilon = 4{\cdot}28$).

Diketolanostanyl Acetate.—(a) *By Clemmensen reduction.* A solution of diketodihydrolanosteryl acetate (5 g.; 1 mol.) in glacial acetic acid (200 ml.) was added to amalgamated zinc (40 g.; 60 atoms), and to the boiling mixture concentrated hydrochloric acid (40 ml.; 30 mols.) was added dropwise within 5 minutes. Vigorous reaction set in and the yellow liquid was decolourised within 10 minutes. Refluxing was continued for a total of 1 hour, and the colourless liquid poured off the zinc, which was extracted once again with boiling acetic acid. The combined acetic acid extracts were poured into water (600 ml.), and the crude product was isolated by extraction with ether, and purified by filtration of its light petroleum solution through a small column of alumina (Brockmann, 15 g.). After 2 crystallisations from chloroform–methyl alcohol *diketolanostanyl acetate*, m. p. 222—224°, was obtained in white lustrous plates. No high-intensity absorption in the near-ultra-violet region of the spectrum; low-intensity maximum at $\lambda = 298$ mμ ($E^{1\%}_{1\,cm.} = 2$) (Found: C, 76·82; H, 10·37. $C_{32}H_{52}O_4$ requires C, 76·80; H, 10·40%); $[\alpha]_D + 54{\cdot}6°$ (*c*, 0·535).

(b) *By reduction with zinc and acetic acid.* To a boiling solution of diketodihydrolanosteryl acetate (2 g.; 1 mol.) in glacial acetic acid (100 ml.), zinc dust (12 g.) was added in portions over a period of 10 minutes and refluxing continued for 1 hour. The colourless acetic acid extracts were poured into water and the product isolated and crystallised as described above. Diketolanostanyl acetate, m. p. 222—224° (1·2 g.), was obtained in colourless lustrous plates (Found: C, 76·70; H, 10·25%), and was further identified by hydrolysis to diketolanostanol, m. p. 183—184°, and oxidation to diketolanostanone, m. p. 165—167° (see below).

(c) *By catalytic hydrogenation.* To diketodihydrolanosteryl acetate (2 g.; 1 mol.) dissolved in glacial acetic acid (120 ml.), platinum oxide (0·5 g.), prepared according to Adams, was added, and the reaction mixture shaken at 70° in an atmosphere of hydrogen for 30 minutes. Hydrogen (80 ml.; 95%) was smoothly absorbed, and the initially deep yellow solution turned colourless within 15 minutes. After removal of the platinum, the product was isolated and gave lustrous crystals of diketolanostanyl acetate, m. p. 222—224° (1·8 g.), from which the alcohol, m. p. 183—184°, and the ketone, m. p. 164—167°, were prepared.

(d) *By reduction with sodium and isopropyl alcohol.* To a boiling solution of diketodihydrolanosteryl acetate (3 g.; 1 mol.) in anhydrous *iso*propyl alcohol (180 ml.), sodium (8 g.; 60 mols.) was added in portions over ½ hour, and the mixture refluxed for a total of 1½ hours. The deep green solution obtained

was evaporated to small bulk under reduced pressure, diluted with water, and neutralised with hydrochloric acid. The crude product separating was extracted with benzene, the combined extracts filtered through a small column of alumina (Brockmann, 6 g.), and the residue, obtained after removal of the solvent, repeatedly crystallised from chloroform–acetone. A small quantity (0·4 g.) of diketolanostanol (see below), m. p. 183—184°, was obtained in minute felted needles (Found : C, 78·70; H, 10·73. $C_{30}H_{50}O_3$ requires C, 78·60; 10·92%).

The combined mother liquors from the alcohol were evaporated under reduced pressure and the crude diketolanostanol acetylated by heating it for 1 hour to 100° with pyridine (20 ml.) and excess of acetic anhydride (12 ml.). Isolation of the product gave colourless plates of diketolanostanyl acetate, m. p. 222—224°. A small quantity of unchanged yellow diketodihydrolanosteryl acetate (m. p. 154—158°) separated from the mother liquors.

Diketolanostanol.—Diketolanostanyl acetate (2 g.) when boiled under reflux for 2 hours with a solution containing potassium hydroxide (8 g.) in ethanol (100 ml.) gave *diketolanostanol*, m. p. 183—184°, in white felted needles (Found : C, 78·42; H, 10·53%); $[\alpha]_D$ + 25·7°, 25·3° (*c*, 0·560, 0·380).

Diketolanostanone.—Diketolanostanol (2 g.; 1 mol.) was dissolved in a mixture of benzene (60 ml.) and glacial acetic acid (10 ml.). To the clear yellow solution, Kiliani's 10% chromic acid solution (20 ml.) was added dropwise, with efficient mechanical stirring during 10 minutes, the temperature of the mixture being maintained below 5° by external cooling. After vigorous shaking for another 15 minutes, the excess of oxidising agent was removed by means of sulphur dioxide. After separation of the benzene layer the aqueous phase was extracted thrice with light petroleum, and the combined extracts washed with sodium hydroxide solution and water, but no acidic oxidation products were removed. The dried light petroleum extracts were filtered through alumina, the solvent removed under reduced pressure, and the residue crystallised thrice from chloroform–methyl alcohol. *Diketolanostanone*, m. p. 165—167°, was obtained in lustrous colourless plates (Found : C, 78·73; H, 10·48. $C_{30}H_{48}O_3$ requires C, 78·95; H, 10·53%); $[\alpha]_D$ + 121·1 (*c*, 0·385).

Diketolanostene.—(a) *From "* α *"-lanostene ("dihydrolanostene").* A solution of lanostene (5 g.; 1 mol.) (prepared from dihydrolanosterol according to Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, **27**, 472; and Dorée *et al.*, *loc. cit.*), in glacial acetic acid (100 ml.), was treated, at 85—90°, with excess of chromium trioxide (5 g.; 4 mols.) in 90% acetic acid (30 ml.), and maintained at 90° for 2½ hours. The excess of oxidising agent was removed with sulphur dioxide, the liquid poured into water (400 ml.), and the yellow product extracted with ether. The combined ethereal extracts were washed with sodium hydroxide solution and water, the solvent removed, and the oily residue, after filtration of its light petroleum solution through a column of alumina (Brockmann, 12 g.), repeatedly crystallised from methyl alcohol. *Diketolanostene*, m. p. 119—120°, was obtained in deep yellow lustrous plates (Found : C, 81·85; H, 10·39. $C_{30}H_{44}O_2$ requires C, 82·19; H, 10·50); ultra-violet absorption spectrum : maximum absorption $\lambda_{max.}$ = 273 mμ; ($E^{1\%}_{1\,cm.}$ = 410).

(b) *From agnostadiene ("* γ *"-lanostene).* Agnostadiene (3 g.; 1 mol.), prepared from dihydroagnosterol (see refs. above), was oxidised with chromium trioxide (3 g., 4 mols.) as before. Crystallisation from methyl alcohol gave diketolanostene, m. p. 119—120°, identical with the product obtained from " α "-lanostene, with which it gave no m. p. depression (Found : C, 81·92; H, 10·45%).

Diketolanostane.—A solution of diketolanostene (2 g.) in glacial acetic acid (80 ml.) was added to amalgamated zinc (15 g.), and to the boiling mixture concentrated hydrochloric acid (15 ml.) added dropwise. After refluxing for 1 hour the product was isolated as described under diketolanostanyl acetate, and gave colourless crystals of *diketolanostane*, m. p. 140—142°. Low-intensity absorption at λ = 298 ($E^{1\%}_{1\,cm.}$ = 3) (Found : C, 81·60; H, 10·72. $C_{30}H_{48}O_2$ requires C, 81·81; H, 10·91%); $[\alpha]_D$ + 104° (*c*, 0·573).

CHELSEA POLYTECHNIC, LONDON, S.W. 3. [*Received, July 1st*, 1947.]

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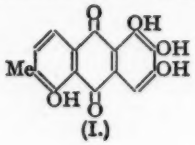
191. *Chemistry of the* Coprosma *Genus. Part III. A Synthesis of Areolatin and an Isomer,* 3 : 5 : 6 : 7-*Tetrahydroxy-2-methylanthraquinone.*

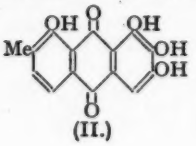
By LINDSAY H. BRIGGS, JACK C. DACRE, and GORDON A. NICHOLLS.

The constitution of areolatin as 1 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone suggested in Part II (this vol., p. 568) has been confirmed synthetically by condensation of 2-hydroxy-*p*-toluic acid with gallic acid in the presence of concentrated sulphuric acid. 3 : 5 : 6 : 7-Tetrahydroxy-2-methylanthraquinone has been isolated as a by-product and characterised.

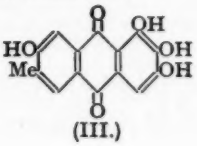
IN Part II (*loc. cit.*) evidence was adduced for the formulation of areolatin, a new anthraquinone colouring matter from the bark of *Coprosma areolata*, as 1 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone (I) although the alternative structure (II) was not rigidly excluded.



(I.)



(II.)



(III.)

It should be possible for condensation of 2-hydroxy-*p*-toluic and gallic acids in the presence of concentrated sulphuric acid to yield compounds corresponding to structures (I) and/or (III) but not (II), so that if by this means a compound is obtained having the properties of areolatin it must have the structure (I). This has proved to be the case.

Self condensation of 2-hydroxy-*p*-toluic acid has been shown (Jowett and Potter, *J.*, 1903, **83**, 1331) to produce the three isomers 1 : 5-dihydroxy-, 3 : 5-dihydroxy-, and 3 : 7-dihydroxy-2 : 6-dimethylanthraquinone, and self condensation of gallic acid yields rufigallic acid (1 : 2 : 3 : 5 : 6 : 7-hexahydroxyanthraquinone) (Robiquet, *Annalen*, 1837, **19**, 204). Condensation of equimolecular quantities of 2-hydroxy-*p*-toluic acid with gallic acid in the presence of concentrated sulphuric acid could therefore give no fewer than six products. The product of this reaction for one hour at 140° was indeed a mixture which could be conveniently separated, however, by chromatographing an acetone solution of it on a magnesium oxide column. Three main bands were obtained, a top purple lake, a middle greyish-green lake, and a lower narrow orange band.

The product from the purple lake was fractionally crystallised from glacial acetic acid to yield areolatin, which must therefore have the structure (I).

The greyish-green lake on decomposition with acid furnished a product which proved to be isomeric with areolatin and must therefore be 3 : 5 : 6 : 7-*tetrahydroxy-2-methylanthraquinone* (III). It was characterised as its *tetra-acetate*, *tetrabenzoate*, and *tetramethyl ether*. With mordanted wool it produces similar colours to those of anthragallol.

The lowest orange band by similar treatment and crystallisation from glacial acetic acid yielded golden yellow needles, m. p. > 330°, which agrees in m. p. and colour reactions with 3 : 5-dihydroxy-2 : 6-dimethylanthraquinone (see above).

By condensation of *m*-hydroxybenzoic acid with gallic acid Noah (*Ber.*, 1886, **19**, 2337) obtained two isomeric products, 1 : 2 : 3 : 5- and 1 : 2 : 3 : 7-tetrahydroxyanthraquinone, one red and the other yellow, but he was unable to distinguish between the two. By analogy with the similar compounds obtained above we suggest that the red and the yellow compound are the 1 : 2 : 3 : 5- and the 1 : 2 : 3 : 7-isomer respectively. We hope to report later on these compounds.

Experimental.

A solution of 2-hydroxy-*p*-toluic acid (3 g., 1 mol.; Meldrum and Perkin, *J.*, 1908, **93**, 1416) and gallic acid (3·36 g., 1 mol.) in concentrated sulphuric acid (20 g., 10 mol.) was heated at 140° for 1 hour. The initial straw colour rapidly changed to red and then to purple which gradually increased in intensity. The dark brown precipitate formed on pouring the reaction mixture into water (300 c.c.) was allowed to settle, collected, washed free from acid, and dried (3·42 g.). It was then extracted with acetone and the black insoluble portion discarded. The acetone solution after being chromatographed on freshly ignited magnesium oxide and developed with the same solvent formed two main bands—a top purple lake and a greyish-green lake—and a narrow orange band at the bottom. The column was extruded and sectioned, and the water-insoluble anthraquinones liberated by dilute hydrochloric acid.

1 : 5 : 6 : 7-*Tetrahydroxy-2-methylanthraquinone* (*Areolatin*).—The product (350 mg.) from the purple band was not homogeneous and contained material from the middle band. This was not unexpected since the first two bands are lakes of magnesium salts which cannot be eluted with organic solvents. The mixture was separated by fractional crystallisation from glacial acetic acid, the sparingly soluble material being identical with that obtained from the second band. The product obtained on concentrating the acetic acid mother liquors, after recrystallisation from glacial acetic acid or better from aqueous acetic acid (charcoal), formed red plates (180 mg.) indistinguishable in its characteristic shrinking point and colour reactions from those of areolatin (Part II). No alteration to the shrinking point occurred on admixture. The tetra-acetate (prepared as in Part II) had m. p. 239° undepressed by an authentic specimen.

3 : 5 : 6 : 7-*Tetrahydroxy-2-methylanthraquinone*.—The dirty brown material (470 mg.) from the greyish-green band, after repeated crystallisation from 60% alcohol, formed orange needles which darkened at high temperatures without melting below 400° (Found : C, 61·8; H, 3·9. $C_{15}H_{10}O_6$ requires C, 63·0; H, 3·5%). In 10% sodium hydroxide solution this 3 : 5 : 6 : 7-*tetrahydroxy-2-methylanthraquinone* gives a green colour changing to reddish-brown on standing in air. The solution in concentrated ammonia is first brown, changing through green to bluish-green. Concentrated sulphuric acid with or without the addition of boric acid gives a deep crimson coloration, and ferric chloride solution gives a dark brown precipitate. When applied to wool mordanted with potassium dichromate, ferric alum, potassium titanium oxalate, stannous chloride, lead acetate, zinc sulphate, or cadmium chloride it produces colours almost identical with those from anthragallol. The *tetra-acetate*, formed by interaction with acetic anhydride in pyridine solution for 2 hours at the boiling point and pouring into water, was crystallised from glacial acetic acid, forming spherical aggregates of light yellow needles of constant m. p. 231—233° (Found : C, 60·4; H, 3·9. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%). The *tetrabenzoate*, prepared as for areolatin tetrabenzoate (Part II), crystallised from glacial acetic acid (charcoal) in pale cream prisms of constant m. p. 218—222° (Found : C, 73·5; H, 3·6. $C_{43}H_{26}O_{10}$ requires C, 73·5; H, 3·7%). The *tetramethyl ether*, also prepared as for the tetramethyl ether of areolatin, formed citron-yellow needles from acetone, m. p. 206·5—207° (Found : C, 66·1; H, 5·5. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

3 : 5-*Dihydroxy*-2 : 6-*dimethylanthraquinone*.—The yellow substance from the orange band crystallised from a large volume of glacial acetic acid (yield, 12 mg.) in minute golden yellow needles, m. p. 330°, which agreed in m. p. and colour reactions with those of 3 : 5-dihydroxy-2 : 6-dimethylanthraquinone, one of the products formed by the self-condensation of 2-hydroxy-*p*-toluic acid (Jowett and Potter, *loc. cit.*).

The analyses are by Drs. Weiler and Strauss, Oxford.

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AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, July 7th*, 1947.]

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192. *Applications of Periodate Oxidation to Some Problems of Carbohydrate Chemistry.*

By D. J. BELL.

A study has been made of the liberation of formaldehyde from primary hydroxyl groups of some partially methylated aldohexoses subjected to periodate oxidation in phosphate buffer at pH 7·5. While 2 : 3-dimethyl glucose, 2 : 3-dimethyl galactose, and 2-methyl glucose rapidly yield theoretical quantities of formaldehyde (determined by the dimedon method), 3-methyl glucose, 2 : 3 : 4-trimethyl glucose, 2 : 4- and 3 : 4-dimethyl galactose, and 3 : 4-dimethyl mannose react more slowly, and the yield of formaldehyde is always considerably below the theoretical. The method is therefore of useful qualitative application, but is not generally available for quantitative purposes.

An attempt has been made to analyse the dimethyl glucose fraction of the cleavage products from two samples of methylated glycogen. This has not been fully successful, although the analytical method employed has been proved to give reliable results on artificial mixtures of the appropriate sugars. The impossibility of effecting complete methylation of glycogen resulting in "extra" dimethyl glucoses appearing on hydrolysis renders the findings inconclusive although there is strong evidence of the presence of a 1 : 3-linkage uniting the "unit-chains".

FOR some time the author has been attempting to elucidate the type of the glycosidic linkage uniting the "unit-chains" comprising the glycogen molecule. As these experiments have now reached a stage where, on the one hand, the available methods of attacking the problem have, in the author's experience, failed to yield absolutely conclusive evidence, while on the other, certain definite experimental observations have accrued, it is considered that a brief report should be made.

The fundamental difficulty experienced in this work lies in the apparent impossibility of effecting complete etherification of the polysaccharide. Although several instances have been encountered where repeated methylation has produced material displaying a methoxyl content closely approaching the expected maximum of 45·6%, analysis by the partition chromatogram (Bell, *J.*, 1944, 473) has revealed that the dimethyl glucose fraction of the hydrolysis products is always in excess of the expected proportion of one mole to every mole of 2 : 3 : 4 : 6-tetramethyl glucose arising from the end-group of each unit chain. Control experiments have shown that the 2 : 3 : 6-trimethyl glucose radical is, to a small extent only (2·2%), demethylated to dimethyl glucoses when subjected to the conditions of hydrolysis employed for methylated glycogen. The amounts of the dimethyl sugar formed in this way, however, do not account for the high yields from methylated glycogen. The origin of this "extra" dimethyl glucose is obscure. A possible explanation may be that some hydroxyl groups are masked by strong hydrogen-bonding. The average molecular weights of (vertebrate) glycogens are very large (Bell, Gutfreund, Cecil, and Ogston, *Biochem. J.*, 1948, **45**, 405), and, since the molecule is roughly spherical in shape, it may be that the methylating reagents are prevented by steric hindrance from penetrating its innermost recesses where the masked hydroxyl groups may lie. The results of experiments on two samples of rabbit glycogen are summarised below.

As it appeared likely that the dimethyl glucose fraction was not homogeneous, the necessity was felt for developing a small-scale method of analysis.

Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476) has described an elegant method of assay for 2 : 3-dimethyl glucose, using gravimetric determination of the formaldehyde liberated by periodate oxidation of the free primary alcoholic group on position 6. Reeves has indicated that it is necessary to carry out the oxidation in the neighbourhood of neutrality, since it has been observed that when using acid periodate 2 : 3-dimethyl glucose does not yield the theoretical

Source of material.	Mol. wt.[1]	OMe (%) after 12 Me_2SO_4–NaOH methylations.	OMe (%) after 3 MeI–Ag_2O methylations.	Hydrolysis products per mole of 2 : 3 : 4 : 6-tetramethyl glucose.[2] 2 : 3 : 6-Trimethyl glucose (moles).[3]	Dimethyl glucose (moles).[3]
Liver	$4{\cdot}4 \times 10^6$	44·9	44·9	9·7	1·3
Muscle	$2{\cdot}6 \times 10^6$	44·2	44·4	8·9	3·2

[1] See Bell, Gutfreund, Cecil, and Ogston (*loc. cit.*).
[2] Separated on chloroform–water partition column.
[3] Values corrected for 2·2% demethylation of 2 : 3 : 6-trimethyl glucose during hydrolysis.

amount of formaldehyde. Since the possible dimethyl glucoses from methylated glycogen must be, with a high degree of certainty, the 2 : 3-, 3 : 6-, and 2 : 6-derivatives, it was decided to investigate their estimation using Reeves's work as the starting point. While this work was in progress, the author learned of the experiments of Jeanloz (*Helv. Chim. Acta*, 1944, **27**, 1509) who had extended Reeves's original observations and had confirmed that a pH near 7 was necessary for quantitative yields of formaldehyde to be obtained from 2 : 3-dimethyl glucose. Both Reeves and Jeanloz have employed the carbon dioxide–bicarbonate buffering system at *ca.* pH 7·5; for the work now described it was decided to employ phosphate buffer of pH 7·5 as this appeared to possess certain manipulative advantages, and when 2 : 3-dimethyl glucose was oxidised alone or in presence of its 3 : 6-dimethyl isomer and of 2 : 6-dimethyl galactose (used in place of the syrupy glucose isomer) quantitative yields of formaldehyde (determined as the dimedon derivative) were obtained. 2 : 6-Dimethyl hexose was determined in the mixtures by first converting the sugars into the ethyl glycopyranosides by boiling ethanol containing hydrogen chloride and then measuring the uptake of periodate by the 3 : 4-glycol grouping of the 2 : 6-dimethyl component. The 3 : 6-dimethyl component could be then determined by difference. Experiments on the determination of formaldehyde by the distillation technique showed that when 2 : 6-dimethyl sugars were present a volatile bisulphite-binding compound was produced in addition to the formaldehyde. This, however, did not form an insoluble dimedon derivative.

Application of the above procedure to the dimethyl glucose fractions from the methylated samples of liver and muscle glycogens yielded the following results.

Source of glycogen sample.	Moles of Me_2 glucose per mole of Me_4 glucose found.	Me_2 glucoses expressed as molar fractions of the total. 2 : 3	2 : 6	3 : 6
Liver	1·3	0·22	0·91	0·17
Muscle	3·2	0·9	1·9	0·4

Since the report of Haworth, Hirst, and Isherwood (*J.*, 1937, 577), which these authors put forward with reserve, it appears to have been generally assumed that the linkage between the unit chains of glycogen concerned position 6 of one of the glucosyl radicals. The above results do not necessarily disprove this for the muscle glycogen specimen, but the very small amount of formaldehyde yielded by the dimethyl fraction from the liver glycogen is a clear indication of a 3-linkage predominating in that material. Until a method is devised for the complete methylation of glycogen it cannot be definitely assumed either that the cross linkages always concern the same position, or, alternatively, that these linkages occur at random on positions 2, 3, or 6.

Having shown that 2 : 3-dimethyl glucose can be easily determined by the formaldehyde-dimedon method, the author studied the possible extensions of the procedure to other partially methylated aldohexoses possessing a free primary alcoholic group. Jeanloz (*loc. cit.*) has found that 2 : 3 : 4-trimethyl glucose, oxidised in his bicarbonate buffer, could not be made to yield more than a fraction of the formaldehyde expected. Similar results were obtained in the present work, using the phosphate buffer, and with 2 : 4- and 3 : 4-dimethyl galactoses, 3 : 4-mannose, and 3-methyl glucose. On the other hand, 2-methyl glucose and 2 : 3-dimethyl galactose yielded the theoretical quantities of formaldehyde-dimedon at the same rate as 2 : 3-dimethyl glucose. The reason for these " anomalous " oxidations is not yet clear, but work in progress in this laboratory has indicated that the action of periodate on partially substituted sugars, and on free sugars themselves, can be modified by the presence of phosphate ion. Indeed, unpublished work (with A. T. Johns and Miss A. Palmer) has so far shown that, at pH 7·5 in phosphate buffer, secondary oxidations result in the production of carbon dioxide

and of steam-volatile acids (largely formic), where such would not be expected normally to be formed. A somewhat similar observation regarding phosphate buffer has already been made by Lindstedt (*Nature*, 1945, **156**, 448) although this author was working at a temperature above that of the laboratory.

No sugar having a free primary hydroxyl group on position 6 and a potential hydroxyl group on position 5 (*i.e.*, the sugar reacts with periodate ion in the open-chain form) failed to yield sufficient formaldehyde-dimedon for satisfactory identification when 10—20 mg. of material were oxidised during 6—12 hours. This procedure, therefore, affords a convenient small-scale method for qualitative detection of a free primary alcoholic group in a partly-methylated sugar. Hitherto the qualitative procedure generally applied has been that of Oldham and Rutherford (*J. Amer. Chem. Soc.*, 1932, **54**, 366) which requires substitution of free hydroxyl groups in the appropriate glycoside by the *p*-toluenesulphonyl radical followed by replacement of the latter by iodine, and, finally, detection of the halogen.

Experimental.

Determination of Formaldehyde from Primary Alcoholic Groups.—The procedure finally adopted owes much to the above-quoted work of Reeves and of Jeanloz. The sugar, or mixture of sugars, is dissolved in water and diluted to a suitable volume so that not more than 20 mg. of sugar having a free primary hydroxyl group are contained in 1—3 ml. The required volume is measured into 10 ml. of phosphate buffer (0·066—0·2M), pH 7·4—7·5, and 6 ml. of 0·1M-sodium metaperiodate (0·6 millimole of 10^{-4}) added. After being kept for the desired time at room temperature (15—17°), the solution is acidified by addition of 1·5 ml. of 2N-hydrochloric acid, and periodate and iodate reduced by the action of 4 ml. of 1·2N-sodium arsenite. When reduction is complete, 16 ml. of 2N-sodium acetate–acetic acid buffer (pH 4·5) are added followed by 160 mg. of dimedon in 2 ml. of ethanol. The mixture is then heated on the boiling water-bath for 10—15 minutes and kept at room temperature for 2 hours.

The crystalline precipitate of formaldehyde-dimedon (hereafter referred to as " FD ") is collected on a tared sintered filter, washed with 75 ml. of water, and weighed after drying for 30—60 minutes at 0·05 mm. over phosphoric oxide.

With dimedon obtained from B.D.H. it was found necessary to run a simultaneous control determination on the reagents as a small precipitate was formed. Material of German origin, however (Merck, " pro analysi "), gave no precipitate.

Experiments on single sugars. Results are tabulated below. In every instance the FD isolated had m. p. 189—190° (corr.).

Sugar.	Duration of oxidation (hrs.).	Sugar taken (mg.).	FD found (mg.).	Yield of FD (%).
2 : 3-Dimethyl glucose	2	9·92	13·8	98·8
,, ,,	2	26·1	35·5	97·0
2 : 3-Dimethyl galactose	2	22·4	30·1	95·8
,, ,,	6	22·4	30·3	96·5
2-Methyl glucose	2	26·4	39·0	98·2
,,	2	22·0	33·0	99·7
3-Methyl glucose	2	31·0	5·2	11·2
,,	4	24·7	6·4	17·2
,,	16	24·7	9·4	25·2
2 : 4-Dimethyl galactose	3	10·38	8·1	56·9
,, ,,	36	10·38	11·7	80·3
3 : 4-Dimethyl galactose	3	8·73	6·1	49·7
,, ,,	48	4·75	5·3	79·9
3 : 4-Dimethyl mannose	8	7·34	2·66	25·8
,, ,,	36	7·34	3·62	35·1
2 : 3 : 4-Trimethyl glucose	2	22·94	13·7	45·4
,, ,,	72	14·48	10·7	56·2

Determination of 2 : 3-Dimethyl Glucose in the Presence of 3 : 6-Dimethyl Glucose and 2 : 6-Dimethyl Galactose.—Experiments showed that syrupy 2 : 6-dimethyl glucose (Bell and Synge, *J.*, 1938, 833) was oxidised without producing formaldehyde; the galactose isomer (Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, **60**, 323; Bell, *J.*, 1945, 692), being crystalline, was, however, used for convenience in the following work. 3 : 6-Dimethyl glucose was prepared by the method of Bell (*J.*, 1935, 175).

(a) *Gravimetric experiments.* 134·23 Mg. of mixed sugars (16·33 mg. of " 2 : 3 ", 87·3 mg. of " 3 : 6 ", and 30·6 mg. of " 2 : 6 "), dissolved in 2 ml. of water and 10 ml. of phosphate buffer, were oxidised for 2 hours with 6 ml. of 0·1M-sodium metaperiodate. After dilution of the mixture to 50 ml. with water, duplicate determinations of FD were carried out on 20 ml. samples. Found: 8·85 mg. (96·2%); 8·72 mg. (94·7%). A control experiment with 45·1 mg. of 3 : 6-dimethyl glucose and 18·0 mg. of 2 : 6-dimethyl galactose yielded no FD.

107 Mg. of mixed sugars (21·55 mg. of " 2 : 3 ", 67·00 mg. of " 3 : 6 ", and 18·50 mg. of " 2 : 6 ") were dissolved in 10 ml. of water, 20 ml. of phosphate buffer, and 24 ml. of 0·1M-periodate. After 2 hours, 40 ml. samples were taken for FD determinations of the 2 : 3-component. Found: 11·88 mg. (98%); 11·69 mg. (96·5%).

(b) *Volumetric experiments.* 84·0 Mg. of mixed sugars (10·0 mg. of " 2 : 3 ", 48·8 mg. of " 3 : 6 ",

and 25·2 mg. of " 2 : 6 ") were oxidised for 2 hours. The solution was diluted to 30 ml., and 15 ml. portions steam-distilled in the Pregl micro-Kjeldahl apparatus following the procedure of Rees (*Biochem. J.*, 1946, **40**, 632) for the determination of hydroxyamino-acids. The amounts of bound bisulphite required 13·38 and 13·09 ml. of 0·01N-iodine respectively. These results indicated that some volatile bisulphite-binding substance had been formed in addition to formaldehyde. Control experiments using 2 : 3-dimethyl glucose alone had previously shown that the formaldehyde formed could be satisfactorily estimated by distillation either titrimetrically, or gravimetrically as FD.

Analysis of a Mixture of the Three Dimethyl Sugars.—69·42 Mg. of mixed sugars (22·44 mg. of " 2 : 3 ", 20·85 mg. of " 3 : 6 ", and 26·13 mg. of " 2 : 6 ") were made up to a volume of 3·00 ml. with pure ethanol. (*a*) Determination of " 2 : 3 ". 1 Ml. of the solution was treated in the usual manner. FD found : 10·00 mg., corresponding to 7·12 mg. of 2 : 3 dimethyl glucose or 21·36 mg. (95·2%) in the original mixture. (*b*) Determinations of " 2 : 6 ". To each of two portions of the solution (1 ml. and 0·835 ml.) were added 2 ml. of pure ethanol containing 2% (w/v) of hydrogen chloride. The mixtures were boiled under reflux for 5 hours, a slight excess of saturated sodium bicarbonate added to each, and the alcohol evaporated on the water-bath. 2 Ml. lots of water were then added to the residues, the pH adjusted to 7 (bromothymol-blue) by dilute acetic acid, and 2 ml. of 0·3325N-sodium metaperiodate added. After 5 hours at room temperature, the periodate consumed was determined by titration with 0·05N-sodium arsenite after addition of 2 ml. of 0·5M-phosphate buffer (pH 7·5) and excess of potassium iodide. A control experiment, omitting the sugars, was run simultaneously. The results were as follows:

Sample taken (ml.).	0·05N-Arsenite consumed (ml.).	2 : 6-Me_2 glycoside in sample (moles).	2 : 6-Me_2 sugar in mixture (mg.).	Recovery (%).
1·00	1·70	0·0425	26·52	101·5
0·835	1·43	0·0358	26·70	102·1

The Demethylating Action of Aqueous Hydrochloric Acid on 2 : 3 : 6-Trimethyl Methylglucoside.—(a) *Preparation of the pure α/β methylglucoside.* A specimen of 2 : 3 : 6-trimethyl glucose which had been twice chromatographed by partition (Bell, *J.*, 1944, 473) was boiled for 4 hours in 5% concentration with methanol containing 2% (w/v) of dry hydrogen chloride. After neutralisation of the acid by addition of barium carbonate and filtration, the solvent was removed under reduced pressure and the residual syrup dried in a vacuum, dissolved in ether, and boiled with charcoal. The syrup obtained after filtration and evaporation of the ether was distilled at 0·05 mm. through a vacuum-jacketed fractionating column. The middle fraction was collected and redistilled, the middle fraction being again collected. This had $[\alpha]_D^{20°}$ + 18·1° (*c*, 7·0 in water; *l* = 4) and $n_D^{16°}$ 1·4566. These constants exactly fit the line given by Hirst and Young (*J.*, 1938, 1247) for the graphical relationships between $[\alpha]_D$ and $n_D^{16°}$ of mixtures of the α- and β-methylglucoside.

(b) *Hydrolysis of the glucoside and chromatography of the products.* The method of hydrolysis was identical with that used in the following experiments on methylated glycogen and has been described, with the partition procedure, by Bell (*J.*, 1944, 473). The following results were obtained:

2 : 3 : 6-Me_3 methyl-glucoside (mg.).	Dimethyl sugars found (mg.).	Methoxyl content of dimethyl sugars (%).	Dimethyl sugars formed (as % of trimethyl sugar expected).
2,330	47	29·6	2·14
2,405	54	29·9	2·34

The mean yield of dimethyl sugars is therefore 2·2%. Analysis showed that the material consisted mainly of the 2 : 6-dimethyl isomer.

Experiment on the Recovery of a Pure Dimethyl Sugar.—Experiments having shown that the recovery of tetramethyl and trimethyl glucose in the partition chromatogram was of the order of 94%, it seemed necessary that a control experiment should be performed using a pure dimethyl sugar. To this end a sample of pure 2 : 3-dimethyl α-methylglucoside (Irvine and Scott, *J.*, 1913, **103**, 575) (560 mg.) was subjected to hydrolysis followed by partition as for a dimethyl sugar. The final acetone solution was evaporated to dryness and the sugar extracted with dry ethyl acetate. Evaporation of the solvent left 496·3 mg. of a colourless glass (94·5% recovery) (OMe, 29·8; 2 : 3-dimethyl glucose by the periodate method, 100%).

Experiments on Glycogen.—(a) *Muscle.* As no previous investigation on rabbit muscle glycogen has been recorded, the following details are appended. (The isolation was performed in 1936.) Rabbits were given lethal doses of " Numal–Roche " and the carcases immediately frozen in ice and salt. 3·5 Kg. of muscle tissue were dissected into 3·5 l. of hot 30% potassium hydroxide. After the tissue had disintegrated the crude glycogen was precipitated by the addition of 4 l. of 95% ethanol. Thereafter purification followed the procedure of Bell and Young (*Biochem. J.*, 1934, **28**, 882). 11 G. of phosphate- and ash-free glycogen were finally obtained, after 4 treatments with acetic acid, representing a tissue-glycogen content of 0·31%. The material, in dilute solution, gave a distinct mauve coloration with iodine, and had $[\alpha]_D$ + 196·0° (*c*, 1·025 in water; *l* = 2).

A sample of this glycogen was acetylated and methylated after Haworth and Percival (*J.*, 1932, 2277). After 8 treatments the methoxyl content was 44·2%; this value was not increased by 4 additional methylations. 3 Methylations with Purdie's reagents, the methylated glycogen being dissolved in dry toluene, likewise failed to effect any further methylation.

Hydrolysis of 1·00 g. followed by partition on the silica–water column gave the following fractions: Me_4, 75 mg.; Me_3, 530 mg.; Me_2, 193 mg. Correcting for 2·2% of the Me_3 fraction appearing as Me_2 by hydrolytic demethylation the final figures become Me_3, 542 mg.; Me_2, 181 mg. Molecular proportions are therefore 1 : 7·7 : 2·4 giving an average unit chain of 11 radicals.

186 Mg. of the dimethyl fraction were dissolved in pure dry ethanol and the solution made up to 10 ml. 2 Ml. of this solution were taken for the determination of 2 : 3-dimethyl glucose. 14·75 Mg. of

FD were found corresponding to 10·5 mg. of the sugar in the sample, or 52·5 mg. (28·2%) in the total. A further 1 ml. of the ethanol solution was converted into the ethyl glucopyranosides as described above. The product consumed 2·15 ml. of 0·05N-periodate corresponding to 11·18 mg. (60%) of 2 : 6-dimethyl glucose. The 3 : 6-dimethyl glucose fraction therefore amounted to 11·8% of the total.

(b) *Liver.* This material had already been examined and reported on (Bell, *Biochem. J.*, 1935, **29**, 2031; *J.*, 1944, 473). 8 Methylations yielded material of OMe 44·7%, a value not raised by 4 further methyl sulphate treatments followed by three with Purdie's reagents in dry toluene. 2·0 G. were hydrolysed and the cleavage products separated by partition to yield the following fractions: Me_4, 199 mg.; Me_3, 1·773 mg.; Me_2, 261 mg. Correcting for 2·2% of the Me_3 fraction appearing as Me_2, by hydrolytic demethylation the final figures become Me_3, 1812 mg.; Me_2, 222 mg. Molecular proportions are therefore 1 : 9·7 : 1·3 giving an average chain length of 12 radicals.

260 Mg. of the dimethyl sugars (OMe, 29·7%) were dissolved in ethanol and the volume made up to 10 ml. 3 × 1 Ml. samples were used for the FD estimation. Found: 6·0, 6·2, and 5·9 mg. corresponding to 4·35 mg. of 2 : 3-dimethyl glucose in the sample of 26·0 mg. of mixed sugars or 16·7% of the total. 1-Ml. samples of the above ethanol solution were used for the 2 : 6-dimethyl glucose determination. Both consumed 3·50 ml. of 0·05N-periodate corresponding to 18·2 mg. (70%) of the sugar. The 3 : 6-isomer was therefore present to the extent of 13·3%.

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193. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part VI.* (+)-cis- *and* (−)-trans-*Cryptol from* (−)-*Cryptone.*

By D. T. C. GILLESPIE, A. KILLEN MACBETH, and JOHN A. MILLS.

Reduction of (−)-cryptone from the oil of *Eucalyptus cneorifolia* by means of aluminium *iso*propoxide gives a mixture consisting of 65% (−)-*trans*-cryptol with 35% of the hitherto unknown (+)-cis-*cryptol*. The separation, purification, and characterisation of the two epimers is described. The alcohols are of interest on account of the unusually high optical rotation and the excellent crystallising power of their derivatives.

THE structure of (−)-cryptone [(−)-4-*iso*propyl*cyclo*hex-2-enone] permits the formation of two epimeric alcohols on reduction by aluminium *iso*propoxide. Galloway, Dewar, and Read (*J.*, 1936, 1595) described a lævorotatory alcohol from this source, and inferred the presence of a second, dextrorotatory form which was not isolated; later Macbeth and Winzor (*J.*, 1939, 264) prepared the enantiomer of the first product above, by reducing (+)-cryptone from water-fennel oil, and proved that their alcohol, and that of Galloway, Dewar, and Read, had the *trans*-configuration. Subsequently, Gillespie and Macbeth (*J.*, 1939, 1531) succeeding in preparing two epimeric DL-cryptols from DL-cryptone, and assigning configurations to each. But hitherto the optically active *cis*-epimers have not been described.

Cooke, Gillespie, and Macbeth (*J.*, 1939, 518) gave a ratio of 95% *trans* to 5% *cis*, but the indirect method of analysis used apparently was unreliable as the investigation of the product of large-scale reductions of (−)-cryptone has now shown that it is a mixture of about 65% (−)-*trans*-cryptol and 35% (+)-cis-*cryptol*, and that there are practically no by-products. The ratio of *trans* to *cis* does not vary much with different proportions of *iso*propoxide to ketone. The proportions present can be calculated from the optical rotation of the crude mixture and derived *p*-nitrobenzoate, and are confirmed by the quantities of epimers actually separated.

In the first instance the *cis*-epimer was separated by means of the allophanates formed on passing cyanic acid into the homogeneous alcohols. The precipitated allophanates were treated with cold chloroform, in which the *trans*-derivative is practically insoluble, and the *cis*-allophanate recovered from the extract was repeatedly recrystallised. Although the method allowed useful exploratory work to be done on the derivatives of the *cis*-alcohol it was later abandoned, as the yield of the *cis*-compound was not good and the purity was questionable.

The separation was ultimately effected by converting the crude cryptols into the *p*-nitrobenzoates. Simple recrystallisation gave a remarkably easy resolution into practically pure *trans*-*p*-nitrobenzoate, and another product containing 80% of *cis*-*p*-nitrobenzoate, which appeared as well-defined mixed crystals not resolved further by recrystallisation. Solubility relationships for the 3 : 5-dinitrobenzoates were more favourable, and permitted the final purification of the *cis*-cryptol. Some mixed crystal formation also seemed to take place with the epimeric 3 : 5-dinitrobenzoates, and likewise the allophanates could not be separated completely by crystallisation although the *cis*-allophanate was far more soluble than the *trans*.

The epimeric cryptols are now readily available and should provide interesting material for optical studies. The high rotations characteristic of the series are illustrated in the table in which all values were determined using 0·1M-solutions. For the esters, but not for the free alcohols, the rotations of the *cis*- and *trans*- forms are nearly equal but of opposite sign, resembling optical antipodes rather than geometrical isomers derived from the same ketone. A more complex but apparently analogous situation in the menthol series has been discussed by Read (*Chem. Reviews*, 1930, **7**, 1).

Rotations of Cryptol Derivatives at 21°.

(All solutions M/10, and in chloroform unless specified.)

Derivative.	$[\alpha]_D$, *trans.*	$[\alpha]_D$, *cis.*	$[M]_D$, *trans.*	$[M]_D$, *cis.*
p-Nitrobenzoate	−171°	+187°	−49,400°	+54,000°
3 : 5-Dinitrobenzoate	−150	+155	−50,000	+51,800
Hydrogen phthalate	−140	+144	−40,300	+41,500
Phenylurethane	−150	+150	−38,900	+38,900
α-Naphthylurethane	−132	+134	−40,800	+41,400
Allophanate (in chloroform)	insol.	+172	—	+39,000
Allophanate (in dioxan)	−136	+141	−30,700	+31,800
Free alcohols (in chloroform)	−118	+ 74	−16,500	+10,400
(−)-Cryptone (in chloroform)	$[\alpha]_D$ −90°, $[M]_D$ −12,400°.			
(−)-Cryptone oxime	$[\alpha]_D$ −106·4°, $[M]_D$ −16,300°.			

The *cis*-configuration assigned to the new epimer was confirmed by its having a higher density and refractive index, and giving lower-melting derivatives, and by the direct reduction of its hydrogen phthalate to *cis*-dihydrocryptol hydrogen phthalate. cis-*Cryptol hydrogen phthalate* was saponified less readily than the *trans*-hydrogen phthalate, but the difference in the rates of saponification was not as great as for the dihydrocryptol hydrogen phthalates (Cooke, Gillespie, and Macbeth, *loc. cit.*).

Optically pure (−)-cryptone was prepared from the pure cryptols in several ways, and a freshly purified specimen with $\alpha_D^{20·8°}$ − 65·9° (homogeneous), $[\alpha]_D^{20°}$ − 91·7° (*c* 2·2 in alcohol), was obtained, which is probably near the maximum attainable rotation. It was impossible to duplicate the high value of $[\alpha]_D$ − 119·3° (*c* 2·0 in alcohol) reported by Galloway, Dewar, and Read (*loc. cit.*), and indeed we have never attained this value in these laboratories with either D- or L-cryptone. Evidently the cryptone in the oil of *E. cneorifolia* is practically optically pure, and does not suffer much racemisation during long keeping or on treating its bisulphite compound with concentrated alkali during the isolation of the ketone. Its oxime, previously reported as a liquid (Berry, Macbeth, and Swanson, *J.*, 1937, 987), was obtained as a solid.

Experimental.

Ponndorf Reduction.—Various samples of crude cryptone up to 8 years old were combined and purified through the bisulphite compound (Berry, Macbeth, and Swanson, *loc. cit.*) and redistilled; b. p. 60°/1 mm., α_D − 64° (homogeneous), $[\alpha]_D$ − 93° (*c* 2·1 in alcohol). Cryptone (92·5 g.) was dissolved in a 0·5M-solution (600 ml., 1·35 equivs.) of distilled aluminium *iso*propoxide in *iso*propyl alcohol, and submitted to 5 hours of slow constant-volume distillation, until the acetone test was negative; reaction was substantially finished in 3 hours. The *iso*propyl alcohol was removed, the residue hydrolysed by ice and 10N-sulphuric acid, and the cryptols extracted and distilled, forming a viscous colourless oil, b. p. 62°/0·3 mm., $\alpha_D^{20°}$ − 46·2° (homogeneous); yield, 94% with little residue.

In subsequent runs the volume of 0·5M-*iso*propoxide solution was varied to give different ratios of *iso*propoxide to cryptone, and with 1·13 equivs. of *iso*propoxide, yield was 91%, $\alpha_D^{20°}$ − 46·8°; with 1·14 equivs., 93%, − 47·8°; with 2·0 equivs., 96%, − 48·2°. The higher ratios gave a faster reaction, and the non-volatile residue was very small.

(−)-trans-*Cryptol.*—The cryptols (72 g.) mixed with pyridine (60 ml.) in dry benzene (100 ml.) were stirred and treated gradually with *p*-nitrobenzoyl chloride (99 g.) in benzene 250 ml.) during 15 minutes at 10—20°. The mixture was held at 20° for 2 hours then refluxed for 1 hour. Removal of pyridine hydrochloride and a little *p*-nitrobenzoic acid, and steam-distillation of benzene and traces of cryptol, left the crude *p*-nitrobenzoate as a waxy yellow solid, melting range 36—65°, $[\alpha]_D^{20°}$ − 34·3° (*c* 2·0 in chloroform); yield, 99%. To ensure a satisfactory separation of the *cis*-epimer, the crude solid was given a preliminary treatment by dissolving it in hot methyl alcohol (1·5—2·0 ml./g.) and slowly cooling to 5°; recovery, 80—85% of pale yellow granules, melting range 37—70°, $[\alpha]_D$ − 51°. This material was divided into 6 parts and recrystallised systematically from methyl alcohol (initially 3 ml./g., later 6 ml./g.), cooling not below 18°. After crystallisation of the head fraction 4 and the tail 10 times, 56% was recovered with m. p. over 80°, and a recrystallisation gave pure (−)-*trans*-cryptol *p*-nitrobenzoate, m. p. 83·4°. Hydrolysis by refluxing for 40 minutes with 4% methyl-alcoholic potassium hydroxide (1·25 mols.) gave (−)-*trans*-cryptol in 93% yield, b. p. 60°/0·5 mm., $\alpha_D^{20°}$ − 136·8° (homogeneous), $d_4^{20°}$ 0·9261, $n_D^{20°}$ 1·4793.

(+)-cis-*Cryptol.*—The mother liquors from all stages except the last in the fractional crystallisation

of the mixed *p*-nitrobenzoates were cooled to 5°, and quickly deposited pale yellow granules, m. p. 35—39°, $[\alpha]_D$ + 104° approximately (chloroform), amounting to 37·5% of the starting material. Recrystallisation from methyl alcohol caused no change in m. p. or rotation. Hydrolysis yielded (96%) an alcohol with $\alpha_D^{22°}$ + 41·2° (homogeneous), corresponding to a mixture of 78% of (+)-*cis*- and 22% of (−)-*trans*-cryptol. This very ready separation of the *p*-nitrobenzoates was confirmed for a mixture of the pure *p*-nitrobenzoates. On dissolving (−)-*trans*-cryptol *p*-nitrobenzoate (4·4 g.) and (+)-cis-*cryptol* p-*nitrobenzoate* (3·7 g.) in methyl alcohol (40 ml.) and cooling to 18°, the solution deposited solid with $[\alpha]_D^{23°}$ − 100° (chloroform) (4·7 g.), then on cooling the mother liquors to 5°, material with $[\alpha]_D^{23°}$ + 109° was obtained (2·0 g.).

The cryptol mixture with $\alpha_D^{22°}$ + 41° was converted into the 3 : 5-dinitrobenzoate by the method described for the *p*-nitrobenzoate, but with 60% more benzene. A practically quantitative yield was obtained, melting range 80—105°, $[\alpha]_D^{20°}$ + 95° (*c* 2·0 in chloroform). Systematic fractional crystallisation in three batches was carried out from methyl alcohol (12 ml./g., later 20 ml./g.), and 6 crystallisations at 20° gave a 38% recovery of material m. p. > 111°. A final recrystallisation from light petroleum (b. p. 90—140°, 6 ml./g.) gave pure (+)-cis-*cryptol* 3 : 5-*dinitrobenzoate* as fine brittle needles, m. p. 112·5—113·5°, $[\alpha]_D^{21°}$ + 155° (*c* 3·3 in chloroform) (Found : C, 57·5; H, 5·5. $C_{16}H_{16}O_6N_2$ requires C, 57·5; H, 5·4%). It is probable that light petroleum would be better than methyl alcohol for the fractional crystallisation.

Hydrolysis of the pure 3 : 5-dinitrobenzoate by boiling it for 20 minutes with 2·5% methyl-alcoholic potassium hydroxide (1·2 mols.) gave a 96% yield of (+)-cis-*cryptol*, a viscous oil with the same strong fragrant odour as the *trans*-epimer, b. p. 70°/1·5 mm., $\alpha_D^{14·5°}$ + 90·2° (homogeneous), $d_4^{30°}$ 0·9293, $n_D^{20°}$ 1·4811.

The methyl alcohol mother liquors from the systematic crystallisation were concentrated, yielding a solid with $[\alpha]_D$ − 47° approx., m. p. 90° (fairly sharp); these properties did not change appreciably in two recrystallisations from methyl alcohol.

Derivatives of Cryptols (rotations in table).—Both cryptols were dehydrated by phthalic anhydride alone at 110°, but could be esterified in excellent yield in pyridine solution at 50—60°. The esters were recrystallised from light petroleum (b. p. 60—90°); (−)-trans-*cryptol hydrogen phthalate* formed colourless thin leaves, m. p. 85—86° (Found : C, 70·8; H, 6·9. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%); (+)-cis-*cryptol hydrogen phthalate* formed large clear prisms, m. p. 68·5—70° (Found : C, 70·9; H, 6·65%). On mixing equivalent quantities of the hydrogen phthalates and piperazine in acetone, the respective *piperazine* salts were obtained; the *trans* formed small shining plates, m. p. 154—156° (decomp.) (Found : N, 4·15. $C_{38}H_{50}O_8N_2$ requires N, 4·25%); the *cis* formed small needles, m. p. 150—151° (decomp.) (Found : N, 4·1%).

The phenylurethanes and α-naphthylurethanes, made by standard methods, were recrystallised from light petroleum (b. p. 40—60° and 60—90°, respectively); the (−)-trans-*phenylurethane* formed silky needles, m. p. 106—107° (Found : C, 74·4; H, 8·1; N, 5·4. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·2; N, 5·4%); the (+)-cis-*phenylurethane* formed very soluble pearly flakes, m. p. 56·5—57·5° (Found : C, 74·1; H, 8·15%); the (−)-trans-α-*naphthylurethane* formed fine white needles, m. p. 118·5—119·5° (Found : C, 77·8; H, 7·3; N, 4·5. $C_{20}H_{23}O_2N$ requires C, 77·6; H, 7·5; N, 4·5%); the (+)-cis-α-*naphthylurethane* was a felt-like mass, m. p. 98—99° (Found C, 77·5; H, 7·4%).

(+)-cis-*Cryptol* p-*nitrobenzoate*, prepared from the pure alcohol, separated from methyl alcohol in glistening scales, m. p. 48·5—49·5° (Found : N, 4·65. $C_{16}H_{19}O_4N$ requires N, 4·85%).

For (−)-*trans*-cryptol 3 : 5-dinitrobenzoate the rotation and melting point were greater than the figures given by Galloway, Dewar, and Read (*loc. cit.*); slender needles from methyl alcohol, m. p. 120—121° (Found : N, 8·65. Calc. for $C_{16}H_{18}O_6N_2$: N, 8·4%).

The cryptols did not react with cyanic acid in ether, benzene, or chloroform solution, but on passing cyanic acid gas into the homogeneous alcohols, conveniently absorbed in glass wool, fair yields of *allophanates* were obtained; the *trans*- formed long needles from chlorobenzene, m. p. 196—197° (efferv.) (Found : C, 58·5; H, 8·1; N, 12·3. $C_{11}H_{18}O_3N_2$ requires C, 58·35; H, 8·0; N, 12·2%); the *cis*- formed minute needles from toluene, m. p. 166—168° (Found : N, 12·5%). From the more soluble portions of the *cis*-allophanate a small yield of (+)-cis-*cryptol urethane* was isolated as small needles from light petroleum, m. p. 118—119° (Found : C, 65·5; H, 9·3; N, 7·6. $C_{16}H_{17}O_3N$ requires C, 65·5; H, 9·35; N, 7·65%). The corresponding *trans*-urethane was not found. As the *trans*-allophanate was practically insoluble in cold chloroform, and the *cis*-allophanate readily soluble, an attempt was made to use these properties as a basis for separation; but the *cis*-cryptol could not be obtained pure in this way.

Oxidation to (−)-*Cryptone*.—Several lots of pure cryptols (4 to 8 g.) were oxidised, using three methods : (*a*) addition of cryptol to Beckmann chromic acid mixture at 55°, (*b*) liberation of chromic acid from potassium dichromate in presence of cryptol, by slow addition of sulphuric acid at 50—60°, (*c*) oxidation with chromium trioxide in acetone, under the conditions used by Bowden, Heilbron, Jones, and Weedon (*J.*, 1946, 39) for the oxidation of oct-3-yn-2-ol. Both *cis*- and *trans*-cryptol gave yields of 75—85% in all cases, $\alpha_D^{16°}$ − 64° to − 65°, but the products did not appear to be homogeneous. The products were mixed, and after conversion into the bisulphite compound and regeneration with alkali, a sample of (−)-cryptone was obtained with b. p. 48°/0·45 mm., $\alpha_D^{20·5°}$ − 65·9° (homogeneous), $[\alpha]_D^{20°}$ − 91·7° (*c* 2·2 in alcohol), $d_4^{30°}$ 0·9352, $n_D^{20°}$ 1·4830.

When (−)-cryptone was allowed to react with hydroxylamine hydrochloride in the presence of sodium carbonate, and the resulting oily oxime was distilled under reduced pressure, a semi-solid product was obtained. Three recrystallisations from light petroleum (b. p. 40—60° at 0°) gave the solid form of (−)-*cryptone oxime* as large plates, m. p. 56·5—57·5° (Found : N, 9·2. $C_9H_{15}ON$ requires N, 9·15%).

Configuration of (+)-cis-*Cryptol*.—(*a*) (+)-*cis*-Cryptol hydrogen phthalate dissolved in glacial acetic acid was shaken with hydrogen in the presence of platinum oxide until somewhat more than the theoretical amount of hydrogen had been absorbed. Dilution of the solution with water and recrystallisation of the product from light petroleum gave *cis*-dihydrocryptol hydrogen phthalate, m. p., and mixed m. p. with an authentic sample, 128—130°. (*b*) The rate of hydrolysis of (+)-*cis*- and

(−)-*trans*-cryptol hydrogen phthalates at 30° was followed in 0·1N-sodium hydroxide, and gave the values: $k^{30°}_{trans}$ 9·08 × 10^{-4}; $k^{30°}_{cis}$ 5·11 × 10^{-4} (mol., $l.^{-1}$, $sec.^{-1}$).

One of us (J. A. M.) wishes to express his thanks for a Federal Research Fellowship which enabled him to take part in the work.

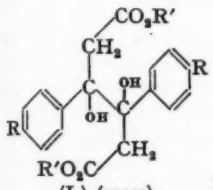
JOHNSON CHEMICAL LABORATORIES, THE UNIVERSITY OF ADELAIDE. [*Received, July 12th*, 1947.]

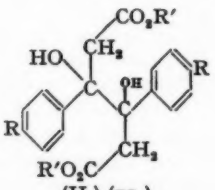
194. *A Modified Synthesis of Chrysene.*

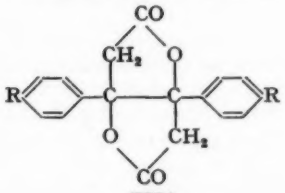
By G. M. BADGER.

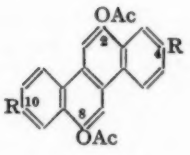
Chrysene, and some chrysene derivatives, have been prepared by modifications of the syntheses by Beschke (*Annalen*, 1911, **384**, 143) and of von Braun and Irmisch (*Ber.*, 1931, **64**, 2461).

IN the original chrysene synthesis by Beschke (*loc. cit.*), a mixture of the isomeric esters (I and II; R = H, R′ = Et) was prepared from benzil by the Reformatsky reaction. The *meso*-ester (I) was converted into a half lactone, hydrolysed, and then reduced with sodium amalgam to ββ′-diphenyl-αα′-dihydromuconic acid, the *trans*-modification of which (V; R = H) was


(I.) (*meso*)


(II.) (DL.)


(III.)


(IV.)

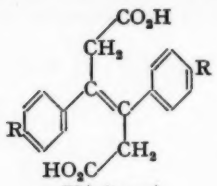
converted into 2 : 8-diacetoxychrysene (IV; R = H). The synthesis by von Braun and Irmisch (*loc. cit.*), the details of which were greatly improved by Ramage and Robinson (*J.*, 1933, 607; see also Lewis, Ramage, and Robinson, *J.*, 1935, 1412), involved the preparation of two stereoisomeric ββ′-diphenyladipic acids (VI and X) by bimolecular reduction of methyl cinnamate, followed by cyclisation and reduction to *cis*- and *trans*-hexahydrochrysene (VIII and XII; R = H). The present method involves the preparation of the ββ′-diphenyladipic acids by reduction of the isomeric diphenyldihydromuconic acids (V and IX), which in turn are prepared by an improved method from the esters (I and II) obtained from benzil by the Reformatsky reaction.

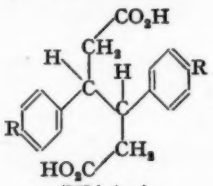
meso-ββ′-Dihydroxy-ββ′-diphenyladipic acid (I; R = H, R′ = H) was reduced with zinc dust and boiling alkali to a mixture of *trans*-ββ′-diphenyl-αα′-dihydromuconic acid (V; R = H), and an isomeric acid, presumably *cis*-ββ′-diphenyl-αα′-dihydromuconic acid (IX; R = H). The dilactone (III; R = H) resulting from the hydrolysis of DL-ββ′-dihydroxy-ββ′-diphenyladipic ester (II; R = H, R′ = Et) was converted into a similar mixture of *cis*- and *trans*-diphenyldihydromuconic acids by the same treatment. Attempted reduction of the *meso*-acid (I, R = R′ = H) with nickel–aluminium alloy and 10% sodium hydroxide (Papa, Schwenk, and Whitman, *J. Org. Chem.*, 1942, **7**, 587) gave only water-soluble derivatives, but similar treatment of the dilactone (III; R = H) gave *meso*-diphenyladipic acid (X; R = H) although not in good yield.

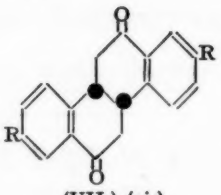
Reduction of *trans*-diphenyldihydromuconic acid (V; R = H) with nickel–aluminium alloy and sodium hydroxide gave DL-diphenyladipic acid (VI; R = H) in good yield. This result is interesting in view of the observation of Schwenk, Papa, Whitman, and Ginsberg (*J. Org. Chem.*, 1944, **9**, 175) that stilboestrol is reduced to a mixture of hexoestrol and *iso*hexoestrol by this method. On the other hand, Docken and Spielman (*J. Amer. Chem. Soc.*, 1940, **62**, 2163) reduced stilboestrol to *iso*hexoestrol (DL-dihydrostilboestrol) quantitatively with hydrogen and Raney nickel in alcohol. Reduction of *cis*-diphenyldihydromuconic acid (IX; R = H) with nickel–aluminium alloy and sodium hydroxide gave *meso*-diphenyladipic acid (X; R = H) almost quantitatively.

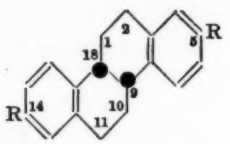
trans-Diphenyldihydromuconic acid has also been converted into 2 : 8-diacetoxychrysene (IV; R = H) and hydrolysed to the dihydroxy-derivative by the method of Beschke (*loc. cit.*). Reduction by the zinc dust–zinc chloride melt method of Clar (*Ber.*, 1939, **72**, 1645) gave chrysene. Diacetoxychrysene was also converted into 2 : 8-diethoxychrysene with sulphuric

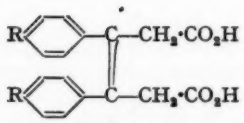
acid and absolute alcohol. Under similar conditions with "alcohol" and sulphuric acid, Beschke obtained 2 : 8-dihydroxychrysene.

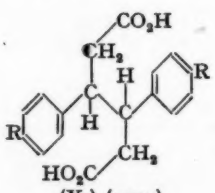

(V.) (*trans*)

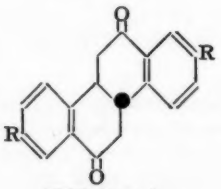

(VI.) (DL)

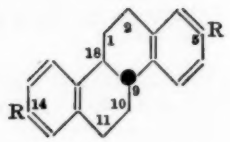

(VII.) (*cis*)


(VIII.) (*cis*)


(IX.) (*cis*)


(X.) (*meso*)


(XI.) (*trans*)


(XII.) (*trans*)

The stereoisomeric diphenyladipic acids (VI and X; R = H) were cyclised to *cis*- and *trans*-diketohexahydrochrysene (VII and XI; R = H) by the method of Ramage and Robinson (*loc. cit.*), and then were reduced to the corresponding hexahydrochrysenes by the Huang–Minlon modification of the Kishner–Wolff method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487).

The Reformatsky reaction with anisil was found to proceed smoothly; but in agreement with Cook and Lawson (*J.*, 1933, 827) only one isomer could be isolated, a considerable quantity of a viscous gum also being formed. The configuration of the ester (I; R = OMe, R′ = Et) is evidently *meso*, for hydrolysis gave ββ′-*dihydroxy*-ββ′-*di*-p-*methoxyphenyladipic acid* (I; R = OMe, R′ = H), and not the dilactone (III; R = OMe) which would be expected from the racemic ester (cf. Beschke, *loc. cit.*). Hydrolysis of the viscous gum, which probably contained some racemic ester in addition to mono-acetic acid derivatives (Cook and Lawson, *loc. cit.*), followed by attempted reduction, also gave intractable gums. Reduction of the *meso*-acid (I; R = OMe, R′ = H) with zinc dust and alkali gave trans-ββ′-*di*-p-*methoxyphenyl*-αα′-*dihydromuconic acid* (V; R = OMe) and an oily acid. The latter, on treatment with nickel–aluminium alloy and sodium hydroxide gave *meso*-di-*p*-methoxyphenyladipic acid (X; R = OMe), but the former could not be reduced by this method, and was recovered unchanged. *trans*-Di-*p*-methoxyphenyldihydromuconic acid was, however, converted into 2 : 8-*diacetoxy*-4 : 10-*dimethoxychrysene* (IV; R = OMe). *meso*-Di-*p*-methoxyphenyladipic acid was cyclised by the Friedel–Crafts method, and the product was reduced to *trans*-5 : 14-dimethoxy-1 : 2 : 9 : 10 : 11 : 18-hexahydrochrysene (XII; R = OMe) by the Huang–Minlon–Kishner–Wolff method.

Experimental.

ββ′-Diphenyl-αα′-dihydromuconic Acid.—(*a*) *meso*-Diethyl ββ′-dihydroxy-ββ′-diphenyladipate was prepared from benzil and ethyl bromoacetate, and separated from the accompanying racemic modification by fractional crystallisation from benzene (Beschke, *loc. cit.*). After hydrolysis with alcoholic potash, the acid (I; R = R′ = H) (10 g.) was dissolved in 2N-sodium hydroxide (200 c.c.) and refluxed with zinc dust (30 g.) for 72 hours. After filtration and acidification, the product was crystallised from alcohol. The first crop (2·5 g.) consisted of *trans-ββ′*-diphenyl-αα′-dihydromuconic acid, m. p. 295—297°. After further recrystallisation, it formed colourless elongated prisms, m. p. 297—299° (decomp.) (Found: C, 73·2; H, 5·2. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%).

The alcoholic liquors, on evaporation, gave a crude acid (1·5 g.) which, after recrystallisation from water, had m. p. *ca.* 170—180°. The diethyl ester prepared from this acid (which was, presumably, *cis-ββ′*-diphenyl-αα′-dihydromuconic acid) with absolute alcohol and sulphuric acid formed colourless needles, m. p. 54—55·5° (Beschke gives m. p. 56°) (Found: C, 75·1; H, 6·7. Calc. for $C_{22}H_{24}O_4$: C, 75·0; H, 6·8%). The pure acid, obtained on hydrolysis of the ester, had m. p. 195° in agreement with Beschke.

(*b*) DL-Diethyl ββ′-dihydroxy-ββ′-diphenyladipate on hydrolysis with alcoholic potash, followed by acidification with acetic acid, gave the dilactone (III; R = H), m. p. 186°. This lactone (5 g.) was refluxed with 2N-sodium hydroxide (150 c.c.) and zinc dust (15 g.) for 72 hours. After treatment as above, it gave the *trans*-acid (1·6 g.) and crude *cis*-acid (2·1 g.). The constitution of the latter was proved in the same manner as above.

DL-*ββ′-Diphenyladipic Acid* (VI).—A solution of the *trans*-acid (V) (3·8 g.) in 10% sodium hydroxide (150 c.c.) was warmed on the steam-bath and treated with nickel–aluminium alloy (15 g.) in small portions. After a further hour on the steam-bath, the filtered solution was added carefully to excess of

concentrated hydrochloric acid, with vigorous stirring. The acid, after recrystallisation from water, formed colourless needles, m. p. 184—186° (3·2 g.) (Found: C, 72·7; H, 6·0. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·0%).

meso-*ββ′-Diphenyladipic Acid* (X).—(*a*) The crude *cis*-acid (IX) was reduced in 80% yield in the same manner as for the *trans*-acid. *meso-ββ′*-Diphenyladipic acid formed colourless needles from alcohol, m. p. 274·5—276·5° (lit., 270—271°) (Found: C, 72·45; H, 6·0. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·0%). The same acid was obtained almost quantitatively by similar treatment of the pure *cis*-acid, regenerated from the ester.

(*b*) A solution of the dilactone (III; R = H) (1 g.) in 10% sodium hydroxide (60 c.c.), on the steam-bath, was treated with nickel–aluminium alloy (10 g.) in small portions. The acidic product was boiled with water (100 c.c.) and rapidly filtered. The water-insoluble product, after recrystallisation from alcohol, had m. p. 271—274° (0·45 g.) not depressed by a specimen of *meso-ββ′*-diphenyladipic acid. The aqueous solution deposited, on cooling, colourless micro-crystals (0·35 g.), m. p. 180—183°, of the original dilactone.

cis-*Hexahydrochrysene.*—DL-Diphenyladipic acid was cyclised with 85% sulphuric acid by the method of Ramage and Robinson (*loc. cit.*). A mixture of the resulting diketone (VII; 0·8 g.), sodium hydroxide (1 g.), hydrazine hydrate (85%, 1 c.c.), and ethylene glycol (15 c.c.) was boiled under reflux for 1 hour. The condenser was then removed and the boiling continued until the temperature reached 195°. After a further period of refluxing for 3 hours, the mixture was cooled, diluted with hydrochloric acid, and extracted with benzene. *cis*-Hexahydrochrysene (0·6 g.) distilled at 118°/0·01 mm., and formed colourless elongated prisms, m. p. 74—75°, from alcohol (Found: C, 92·3; H, 7·7. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%).

trans-*Hexahydrochrysene.*—*meso*-Diphenyladipic acid was cyclised as above. The *trans*-diketone (XI; 1 g.) was reduced as for the *cis*-isomeride, and gave 0·72 g. of *trans*-hexahydrochrysene, b. p. 150°/0·15 mm., m. p. 114—115° (Found: C, 92·2; H, 7·7. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%).

2 : 8-*Diethoxychrysene.*—A suspension of 2 : 8-diacetoxychrysene (1·5 g.) (Beschke, *loc. cit.*) in absolute alcohol (60 c.c.) and sulphuric acid (7·5 c.c.) was refluxed for 2 hours. After cooling, the crystalline 2 : 8-diethoxychrysene was collected (1·1 g.) and recrystallised from acetic acid, forming colourless needles, m. p. 207—208° (Found: C, 83·35; H, 6·2. Calc. for $C_{22}H_{20}O_2$: C, 83·5; H, 6·3%). Beschke gives m. p. 207°.

Chrysene.—A mixture of 2 : 8-dihydroxychrysene (0·85 g.), zinc dust (2 g.), sodium chloride (2 g.), and zinc chloride (10 g.) was heated at about 300° for ½ hour. The melt was extracted with hydrochloric acid, warm dilute sodium hydroxide, and hot water. After sublimation at 200°/0·1 mm., the product (0·28 g.) had m. p. 250—251° alone or mixed with authentic chrysene. The alkaline liquors, on acidification, gave 0·24 g. of crude dihydroxychrysene.

meso-*ββ′-Dihydroxy-ββ′-di*-p-*methoxyphenyladipic Acid.*—The ester (I; R = OMe, R′ = Et) (Cook and Lawson, *loc. cit.*) was hydrolysed with alcoholic potash to the *acid*, which formed colourless elongated prisms, m. p. 187—188° (decomp.), from alcohol (Found: C, 61·6; H, 5·7. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·6%).

ββ′-Di-p-*methoxyphenyl-aa′-dihydromuconic Acid.*—A solution of the ester (I; R = OMe, R′ = Et) (10 g.) in alcohol (50 c.c.), water (25 c.c.), and potassium hydroxide (12 g.) was refluxed for 2 hours. After removal of the alcohol, water (50 c.c.), 2N-sodium hydroxide (150 c.c.), and zinc dust (30 g.) were added, and the mixture refluxed for 65 hours. The acidic product was dissolved in hot alcohol, from which trans-*ββ′-di*-p-*methoxyphenyl-aa′-dihydromuconic acid* (2·1 g.) was obtained as colourless prisms, m. p. 252—254° (decomp.) (Found: C, 67·6; H, 5·5. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%). The alcoholic liquors, on evaporation, gave an oil which could not be induced to crystallise. After dissolution of this in 10% sodium hydroxide (120 c.c.) and heating on the steam-bath, nickel–aluminium alloy (12 g.) was added in small portions. The filtered solution, added slowly to excess of hydrochloric acid with vigorous stirring, gave *meso-ββ′*-di-*p*-methoxyphenyladipic acid, m. p. 255—257° from butanol (lit., 250°), yield 3·1 g. (Found: C, 67·3; H, 6·3. Calc. for $C_{20}H_{22}O_6$: C, 67·0; H, 6·15%).

trans-5 : 14-*Dimethoxy*-1 : 2 : 9 : 10 : 11 : 18-*hexahydrochrysene.*—*trans*-Diketodimethoxyhexahydrochrysene (XI; R = OMe; 1·2 g.), prepared from *meso-ββ′*-di-*p*-methoxyphenyladipic acid by the method of Ramage and Robinson, (*loc. cit.*), was reduced with hydrazine hydrate (85%; 1·5 c.c.), sodium hydroxide (1·2 g.), and ethylene glycol (15 c.c.) as described for hexahydrochrysene. The product was sublimed at 180°/0·1 mm. and recrystallised from acetic acid to form colourless needles, m. p. 184—185° (lit., 185°). Yield, 0·75 g.

2 : 8-*Diacetoxy*-4 : 10-*dimethoxychrysene.*—*trans*-Di-*p*-methoxyphenyldihydromuconic acid (0·5 g.) was suspended in acetic anhydride (3 c.c.), and concentrated sulphuric acid (0·15 c.c.) added with cooling. After ½ hour, the solid (0·4 g.) was collected, washed with acetic acid, and recrystallised from acetic acid. 2 : 8-*Diacetoxy*-4 : 10-*dimethoxychrysene* formed colourless silky needles, m. p. 275—276° (decomp.)(Found: C, 71·5; H, 5·2. $C_{24}H_{20}O_6$ requires C, 71·3; H, 5·0%).

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195. *The Elimination of Sulphur in certain Reductions of the 2 : 2′ : 4 : 4′-Tetranitrodiphenyl Mono- and Di-sulphides, and an Alternative Route to the Preparation of Some 5-Substituted Benz-1-thia-2 : 3-diazoles.*

By Herbert H. Hodgson and Douglas P. Dodgson.

2 : 2′ : 4 : 4′-Tetranitrodiphenyl sulphide is found to be best prepared by a two stage process of the Twiss reaction of sodium thiosulphate on 1-chloro-2 : 4-dinitrobenzene, and the disulphide by interaction of the last compound with sodium disulphide at as low a temperature as possible, both reactions being carried out in aqueous ethanol. Attempted reduction with iron replaced sulphur by hydrogen and afforded *m*-phenylenediamine from both the mono- and the di-sulphide. The disulphide was reduced by zinc and 90% aqueous acetic acid, but the monosulphide only gave a blue compound of high m. p. The 2 : 4-diamino-thiol produced from the disulphide gave with nitrous acid a benz-1-thia-2 : 3-diazole-5-diazonium salt which was converted into various 5-substituted benz-1-thia-2 : 3-diazoles; the overall yields of the 5-halogeno-compounds were somewhat higher than *via* 5-nitrobenz-1-thia-2 : 3-diazole.

Twiss found (*J.*, 1914, **105**, 1678) that when 1-chloro-2 : 4-dinitrobenzene reacted with sodium thiosulphate in aqueous ethanol a mixture of 2 : 2′ : 4 : 4′-tetranitrodiphenyl mono- and di-sulphides was formed in which the former greatly preponderated. It has now been found that the yield of the monosulphide is improved by the addition of the sodium thiosulphate in two batches. Alternatively, a somewhat increased yield is obtained by the action of sodium sulphide on 1-chloro-2 : 4-dinitrobenzene in aqueous ethanol. For the preparation of the disulphide, a somewhat modified method of Claas (*Ber.*, 1912, **45**, 753) has been adopted whereby 1-chloro-2 : 4-dinitrobenzene is treated with sodium disulphide in aqueous ethanol at as low a temperature as possible; this involves a much greater dilution than that employed by Claas, but the product at the minimum temperature was much lighter yellow than that at higher temperatures.

The reduction of both the mono- and the di-sulphide varied according to the reagent employed. The neutral iron powder method of Hodgson and Marsden (*J.*, 1944, 398) proved difficult to manipulate owing to the resistance offered to wetting by the organic nitro-compound, and the usual Béchamp process of iron and dilute sulphuric acid resulted in complete removal of sulphur from both the mono- and the di-sulphide with replacement by hydrogen and formation of *m*-phenylenediamine. The fate of the sulphur was not investigated, but, although the yields of *m*-phenylenediamine did not account for the whole of the tetranitro-compound, no trace of an organic sulphur compound could be found. Reduction by stannous chloride in hydrochloric acid solution also resulted in the removal of sulphur. This scission of sulphur linkages is a known but little investigated phenomenon, and, in the so-called " sweetening " practice in petroleum refining, sulphur is removed by treatment of the oil with iron or a similar metal at high temperatures, a process which in some cases may involve catalytic reduction. Lankelma and Knauf (*J. Amer. Chem. Soc.*, 1931, **53**, 309) also found that in the reduction of 4 : 4′-dichloro-2 : 2′-dinitrodiphenyl disulphide with tin and hydrochloric acid there was considerable elimination of sulphur particularly at boiling temperatures, and in consequence the reaction had to be carried out at about 70° (cf. Baxter and Spring, *Ann. Reports*, 1945, **42**, 99—101).

Finally, zinc dust in glacial acetic acid, containing a small quantity of water to avoid the possibility of concurrent acetylation, was found to be the most satisfactory method for the reduction of 2 : 2′ : 4 : 4′-tetranitrodiphenyl disulphide; the only disadvantage was the comparatively large amount of acetic acid required for good filtration. Reduction with sodium dithionite (hydrosulphite) was less convenient and not more efficient.

From 2 : 2′ : 4 : 4′-tetranitrodiphenyl monosulphide a blue compound containing nitrogen and sulphur—probably a highly complex mixture of thiazine-like compounds—was obtained. This recalls the similar observation by Leigh (Thesis, University of London, Nov., 1939, p. 16) that attempts to reduce 4 : 4′-dinitro-1 : 1′-dinaphthyl sulphide gave only an unidentifiable insoluble deep blue substance.

The 2 : 4-diaminophenylthiol, obtained by reduction of the disulphide as above, was characterised by its *dihydrochloride* and its *triacetyl* derivative, and was converted by diazotisation (Hodgson and Walker, *J.*, 1933, 1620) followed by the usual procedures into 5-chloro-, 5-bromo-, 5-iodo-, and 5-hydroxy-benz-1-thia-2 : 3-diazole, and (in 65% yield) into benz-1-thia-2 : 3-diazole-5-azo-β-naphthol. The overall yields of the 5-substituted benz-1-thia-2 : 3-diazoles (*ca.* 30%), prepared in this way from 1-chloro-2 : 4-dinitrobenzene as initial material, are greater than by the processes already described by Hodgson and Dodgson (this vol., p. 870) from 5-nitrobenz-1-thia-2 : 3-diazole (*ca.* 12% from the same initial material) by virtue of the

fewer stages involved. Further, the solid benz-1-thia-2 : 3-diazole-5-diazonium sulphate was isolated by the method of Hodgson and Mahadevan (*J.*, 1947, 325), and thereby facilitates the preparation of the numerous compounds for which diazo-compounds are used as intermediates.

2 : 4-Diaminophenylthiol has been mentioned previously but not isolated or identified (Pollack, Riesz, and Riesz, *Monatsh.*, 1931, **58**, 129).

Experimental.

2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphide.*—(a) *Thiosulphate process.* To a solution of 1-chloro-2 : 4-dinitrobenzene (40·5 g., 0·2 g.-mol.) in ethanol (350 c.c.) was added one of sodium thiosulphate (50 g., 0·2 g.-mol.) in water (200 c.c.), and the mixture was refluxed for an hour. The yellow crystalline sulphide was filtered off from the hot solution, and sodium thiosulphate (20 g.) was added to the filtrate which was again refluxed for 30 minutes. After cooling, the second precipitate of sulphide was removed and added to the first; total yield, 28 g. (76%), m. p. 193—195° raised to 197° on recrystallisation from glacial acetic acid (Twiss, *loc. cit.*, gives m. p. 193°) (Found : S, 9·0. Calc. for $C_{12}H_6O_8N_4S$: S, 8·7%).

(b) *Sodium sulphide process.* To a stirred solution of 1-chloro-2 : 4-dinitrobenzene (40·5 g.) in ethanol (400 c.c.) was added one of sodium sulphide nonahydrate (24 g., 0·1 g.-mol.) in ethanol (60 c.c.) and water (40 c.c.); when the red colour produced had disappeared, this being hastened by moderate heating towards the end of the reaction, the crystalline sulphide was filtered off and washed in sequence with 5% aqueous sodium hydroxide, water, 5% hydrochloric acid, and water; yield, 29 g. (79%) of a product somewhat browner than that from (a), especially when the reaction was carried out at higher temperatures; this colour was difficult to remove.

2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphoxide.*—2 : 2′ : 4 : 4′-Tetranitrodiphenyl sulphide (0·9 g.) was oxidised by keeping it for an hour at room temperature in nitric acid (10 c.c., *d* 1·5). On dilution with water, the precipitate of the *sulphoxide* crystallised from ethanol in long pale yellow prisms, m. p. 190° (mixed m. p. with initial material, 170—189°) (Found : S, 8·5. $C_{12}H_6O_9N_4S$ requires S, 8·4%).

Reduction of 2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphide.*—(a) *With iron powder and sulphuric acid.* The sulphide (3·66 g.) was made into a paste with iron powder (14 g., pin dust) and 5% aqueous sulphuric acid (5 c.c.), and, when frothing had ceased, ethanol (3 c.c.) was added and the mixture refluxed on an oil-bath for 3 hours with occasional stirring. Charcoal and ethanol (15 c.c.) were then added, the heating continued for a further 30 minutes, ammonia (2·5 c.c., *d* 0·88) added, and the stirred mixture cooled and filtered. The residue was extracted with boiling ethanol (30 c.c.), the extract added to the previous filtrate, followed by hydrochloric acid (4 c.c., *d* 1·18). After concentration to 10 c.c. and cooling, the dihydrochloride of *m*-phenylenediamine (2·25 g.) crystallised and was identified by its diacetyl and tribromo-derivatives, and also by bisdiazotisation and conversion into 1 : 3-di-iodobenzene.

(b) *With stannous chloride and hydrochloric acid.* The sulphide (18·3 g.) was added portionwise to a solution of crystallised stannous chloride (120 g.) in concentrated hydrochloric acid (125 c.c., *d* 1·18) at 70°. Each batch dissolved readily with no appreciable colour change, and, after complete dissolution, the tin was removed from the solution by hydrogen sulphide, the volume reduced to 10 c.c., and the dihydrochloride of *m*-phenylenediamine (2·5 g.) which separated was removed and identified as above.

(c) *With zinc dust and acetic acid.* A mixture of the finely powdered sulphide (7·3 g.) and zinc dust (24 g.) was carefully stirred with 90% aqueous acetic acid (150 c.c.) added gradually; an intense blue colour appeared immediately and the liquid boiled vigorously. When the boiling had ceased, the mixture was filtered, the filtrate made alkaline with ammonia, and the blue precipitate collected; it contained nitrogen and sulphur and did not melt below 300°. This complex was very sparingly soluble in the usual solvents and in dilute hydrochloric acid; its solution in concentrated sulphuric acid was intense blue, changing to maroon on dilution with water.

2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Disulphide.*—(a) *Thiosulphate process.* After removal by filtration of the monosulphide (see above), air was bubbled through the filtrate until the disulphide (2·5 g., 6·5%) was completely precipitated.

(b) *Sodium disulphide process.* A stirred solution of 1-chloro-2 : 4-dinitrobenzene (40·5 g.) in ethanol (250 c.c.) below 30° was treated gradually with a solution of crystallised sodium sulphide (24 g., 0·1 g.-mol.) and sulphur (3·2 g., 0·1 g.-mol.). At each addition the mixture became transitorily red, and a yellow-brown precipitate rapidly formed. A small amount of heat was evolved, and on completion of the addition the mixture was heated on the water-bath until no red colour remained; it was then filtered, and the light yellow residue of the crude disulphide was extracted with hot glacial acetic acid and then washed in sequence with water, hot 5% aqueous hydrochloric acid, water, hot 5% aqueous sodium hydroxide, and hot water; yield, 33 g., 83%. It crystallised from hot pyridine or aniline, but for all experimental purposes the crude product was sufficiently pure; it exploded at *ca.* 300° (Claas, *Ber.*, 1912, **45**, 753, gives 303°). Reaction at initial boiling temperatures is more rapid, but the product is browner (Found : S, 15·7. Calc. for $C_{12}H_6O_8N_4S_2$: S, 16·1%).

Reduction of 2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Disulphide.*—(a) *By iron powder and sulphuric acid, and* (b) *by stannous chloride and hydrochloric acid.* Experimental details are as for the monosulphide. In each process sulphur was eliminated with formation of *m*-phenylenediamine, which was identified as above.

(c) *By sodium dithionite* (*hydrosulphite*). The disulphide (4 g.), suspended in hot 15% aqueous sodium hydroxide (100 c.c.) was treated gradually with sodium dithionite (64 g.), and the mixture then refluxed for 30 minutes, cooled, and treated with sulphuric acid (25 c.c., *d* 1·84); after 30 minutes the precipitated sulphur was filtered off and the filtrate stirred gradually into a solution of sodium nitrite (3 g.) in sulphuric acid (20 c.c., *d* 1·84) maintained below 10°. After an hour, the solution was poured into cold hydrochloric acid (160 c.c., *d* 1·18) containing cuprous chloride (16 g.), and, when reaction had ceased, the mixture was diluted with water and steam distilled. Yield of 5-chlorobenz-1-thia-2 : 3-diazole, 0·8 g. (24%).

(d) *By zinc dust and acetic acid.* A mixture of the disulphide (4 g.) and zinc dust (12·8 g.) was stirred into 90% aqueous acetic acid (100 c.c.), and, after the initial evolution of heat had ceased, the whole was carefully raised to the boil, refluxed for 30 minutes, filtered hot, and the residue washed with hot 90% acetic acid (50 c.c.). The two filtrates were combined, and saturated at 0° with dry hydrogen chloride, after which ether (400 c.c.) was added at 0°; a white precipitate of 2 : 4-*diaminophenylthiol dihydrochloride* (3 g., 71% yield) formed gradually. This was filtered off, washed with ether, dissolved in the minimum amount of water (15 c.c.), reprecipitated by saturation of the ice-cold solution with hydrogen chloride, filtered off, washed with ether, and dried. The pale yellow compound was readily soluble in water, less so in ethanol, and quite stable in air; m. p. > 300° (Found: S, 14·7. $C_6H_8N_2S,2HCl$ requires S, 15%).

2 : 4-*Diacetamidophenyl thiolacetate* was obtained when a solution of the above hydrochloride (1 g.) in pyridine (2 c.c.) was heated with acetic anhydride (2 c.c.) on the water-bath for 30 minutes, cooled, and stirred into 4% aqueous hydrochloric acid (20 c.c.). After several days, with periodic scratching, the colourless triacetyl compound separated; it crystallised from ethanol in silvery plates, m. p. 245° (decomp.) (Found: S, 12·3. $C_{12}H_{14}O_3N_2S$ requires S, 12·0%), which were readily soluble in the usual organic solvents, slightly soluble in hot water, but insoluble in cold aqueous sodium hydroxide.

Reactions of 2 : 4-*Diaminophenylthiol.*—The hydrochloride (1 g.) was suspended in glacial acetic acid (5 c.c.) and the mixture stirred gradually into a solution of sodium nitrite (0·7 g.) in sulphuric acid (4 c.c., *d* 1·84) maintained below 10°; some hydrogen chloride was evolved at this stage, but did not interfere with the reaction. The acid solution was next poured on ice (20 g.), and the free nitrous acid removed by urea (0·3 g.), after which potassium iodide (3·3 g.) was added, the mixture subsequently made alkaline with aqueous sodium hydroxide, and steam distilled. The 5-iodobenz-1-thia-2 : 3-diazole, which passed over, crystallised from 80% aqueous methanol in small cubes, m. p. and mixed m. p. with authentic specimen (Hodgson and Dodgson, *loc. cit.*) 103°.

Diazotisation of the Zinc–Acetic Acid Reduction Liquor Above.—Batches of 2 : 2′ : 4 : 4′-tetranitrodiphenyl disulphide (4 g.) were reduced and the mixtures filtered as above; sulphuric acid (6 c.c., *d* 1·84) was added to each mixture which was then cooled to *ca.* 10°, at which point solidification began, and stirred into a solution of sodium nitrite (3 g.) in sulphuric acid (14 c.c., *d* 1·84) below 10°. The resulting mixtures were treated as follows: (*a*) Coupled with β-naphthol after dilution with water, to give benz-1-thia-2 : 3-diazole-5-azo-β-naphthol (4·1 g., 67%). (*b*) Added separately to solutions of cuprous chloride (12 g.) in hydrochloric acid (120 c.c., *d* 1·18), and cuprous bromide (17 g.) in hydrobromic acid (120 c.c., *d* 1·7), which were then steam distilled to give 5-chloro- (1 g., 30%) and 5-bromo- (1 g., 23%) benz-1-thia-2 : 3-diazole respectively; also diluted with ice–water, free nitrous acid removed by urea (1·5 g.), potassium iodide added (6·6 g.), and the mixture steam distilled for 5-iodobenz-1-thia-2 : 3-diazole to pass over. (*c*) Diluted with ice–water until all the salts had dissolved, kept overnight, then gradually heated to boiling, cooled, and extracted with ether; the extract was washed with aqueous sodium hydrogen carbonate to remove acidity, and then shaken with 10% aqueous sodium hydroxide (10 c.c.) to remove the 5-hydroxybenz-1-thia-2 : 3-diazole (0·8 g., 26% yield) which was precipitated from the alkaline extract on acidification and recrystallised from hot water in yellow needles, m. p. and mixed m. p. with authentic specimen (Hodgson and Dodgson, *loc. cit.*) 161°.

Before addition of the acetic acid solution of the amine to the nitrosylsulphuric acid it was concentrated to 60 c.c., and, after diazotisation, the acid solution was treated with ether (200 c.c.); after an hour the yellow benz-1-thia-2 : 3-diazole-5-diazonium sulphate was collected and washed with ether; it only slowly turned brown in air, and on addition to 10% aqueous sodium hydroxide (200 c.c.) containing β-naphthol (4 g.), gave a precipitate of benz-1-thia-2 : 3-diazole-5-azo-β-naphthol (0·7 g., 11%) which was crystallised and identified (cf. Hodgson and Dodgson, *loc. cit.*).

A solution of *m*-phenylenediamine (2·16 g.) in glacial acetic acid (15 c.c.) was stirred gradually into one of sodium nitrite (3·2 g.) in sulphuric acid (32 c.c., *d* 1·84) below 30°. When diazotisation was complete, the mixture was poured into sufficient ice-water to give a clear solution, which was filtered and then stirred into 20% aqueous sodium hydroxide (400 c.c.) containing β-naphthol (10 g.) and ice (200 g.). After being kept at 0° until coupling was complete, the mixture was heated to 50° to coagulate the precipitate of the benzene-1 : 3-bisazo-β-naphthol, which was removed and washed with hot 2% aqueous sodium hydroxide and water; it crystallised from glacial acetic acid (charcoal) in very dark green crystals (red in transmitted light), m. p. 265° (Schoutissen, *Rec. Trav. chim.*, 1935, **54**, 381, gives m. p. 251°) (Found: N, 13·6. Calc. for $C_{24}H_{18}O_2N_4$: N, 13·4%).

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196. *Improved Preparations of* 3 : 3′-*Dinitro- and* 3 : 3′-*Diaminodiphenylamine, together with Some Derivatives.*

By HERBERT H. HODGSON and DOUGLAS P. DODGSON.

3 : 3′-Diaminodiphenylamine has been prepared for the first time in quantity, and in over 90% yield, by the neutral reduction of 3 : 3′-dinitrodiphenylamine with iron powder (cf. Hodgson and Marsden, *J.*, 1944, 398). The 3 : 3′-dinitro-compound has also been obtained in much improved yield. *N*-Benzoyl-3 : 3′-dinitrodiphenylamine has been successfully reduced by the iron powder method without removal of the benzoyl group.

3 : 3′-DINITRODIPHENYLAMINE has been obtained in 70% yield from 3-bromonitrobenzene and 3-nitroacetanilide by a modification of the conditions employed by Albert and Linnell (*J.*, 1936, 88) in the Goldberg synthesis for substituted diphenylamines (*Ber.*, 1907, **40**, 4541). The use of 3-chloro- instead of 3-bromo-nitrobenzene gave a reduced yield of a cruder product.

3 : 3′-Dinitrodiphenylamine was readily acetylated and benzoylated, but under the same conditions *p*-toluenesulphonyl chloride failed to react with it. Various thionating conditions were used in an unsuccessful attempt to cyclise the diphenylamine with a sulphur bridge, but without success; *viz.*, by heating the amine with sulphur alone, sulphur and aluminium chloride, thionyl chloride, and thionyl chloride with aluminium chloride, in the first two cases at temperatures up to 250°, and in the last two cases with excess of thionyl chloride at the boiling point; in all these reactions the initial compound was recovered unchanged.

In view of the ease with which 3 : 3′-diaminodiphenylamine is oxidised either when heated in air or in various reactions, the N-*benzoyl* derivative was made by benzoylation of 3 : 3′-dinitrodiphenylamine and reduction of the nitro-groups by the neutral iron powder method of Hodgson and Marsden (*J.*, 1944, 398), whereby an almost theoretical yield was obtained; it was identified by hydrolysis with 10% hydrochloric acid to benzoic acid and 3 : 3′-diaminodiphenylamine, and by bisdiazotisation and subsequent coupling with β-naphthol.

3 : 3′-Diaminodiphenylamine was prepared from the dinitro-compound in yields of over 90% by the neutral iron reduction method of Hodgson and Marsden (*loc. cit.*). Other attempts at reduction, including the method adopted by Albert and Linnell, who do not report yields and who worked with 0·2 g., and also that of reductive acetylation with zinc dust in acetic anhydride–glacial acetic acid–sodium acetate, afforded either very poor yields or produced tarry material which was difficult to resolve. Moreover, the colourless product obtained by the iron method was very stable in air and only slowly turned brown in the course of several months. The other properties reported by Albert and Linnell (*loc. cit.*) for the amine and the ease of resinification of the diacetyl derivative are confirmed. The diglycine [3 : 3′-*di*-(ω-*carboxymethylamino*)*diphenylamine*] was readily obtained by the action of sodium chloroacetate on 3 : 3′-diaminodiphenylamine, but attempts at decarboxylation to 3 : 3′-bismethylaminodiphenylamine (cf. Henesey, *J. Soc. Dyers and Col.*, 1938, **54**, 66) were unsuccessful.

EXPERIMENTAL.

Preparation of 3 : 3′-*Dinitrodiphenylamine.*—3-Bromonitrobenzene (40·4 g., 0·2 g.-mol.) and 3-nitroacetanilide (18 g., 0·1 g.-mol.) were refluxed in nitrobenzene solution (200 c.c.) for 16 hours in the presence of anhydrous potassium carbonate (14 g.) and cuprous bromide (0·5 g.), after which the nitrobenzene and unchanged 3-bromonitrobenzene were removed by steam. The tarry residue was solidified by keeping it at 0° for a short time, powdered, thoroughly washed with water at the pump, and extracted thrice with boiling ethanol (300 c.c. each time). The extract was filtered, concentrated to 300 c.c., refluxed for an hour after the addition of hydrochloric acid (45 c.c., *d* 1·18), and poured on ice (500 c.c.), and the precipitated crude reddish-brown 3 : 3′-dinitrodiphenylamine was filtered off after it had coagulated, and washed with hot water until the washings were clear; yield, 18·7 g., 72%. The compound separated from ethanol (charcoal) in small orange plates, m. p. 188° (Albert and Linnell, *loc. cit.*, give m. p. 186·5°) (Found: N, 16·5. Calc. for $C_{12}H_9O_4N_3$: N, 16·2%), which were readily soluble in cold pyridine and nitrobenzene, slightly so in cold chloroform, glacial acetic acid, ethanol, ether, and toluene, and insoluble in ligroin; in concentrated sulphuric acid, the solution had a slight greenish tint (which was emphasised by the addition of a drop of nitric acid), and on dilution with water it afforded a pale yellow suspension which had a slight green fluorescence. Attempts to prepare this compound by interaction of 3-nitroaniline and its hydrochloride were unsuccessful since at the point when reaction commenced (*ca.* 180°), as shown by the sublimation of ammonium chloride, more profound reactions also occurred, and at *ca.* 210° the mass began to evolve heat and decompose into a deep blue complex which could not be identified. After removal of unchanged 3-nitroaniline with hot dilute hydrochloric acid, even before the stage of vigorous decomposition, the blue substance of m. p. 200—230° (from glacial acetic acid) was an invariable product, and, from its colour and solubility in concentrated hydrochloric acid, it would appear to be of a diphenazine type; 3 : 3′-dinitrodiphenylamine was not isolated from any of the experiments.

N-*Acetyl*-3 : 3′-*dinitrodiphenylamine* was obtained when a mixture of 3 : 3′-dinitrodiphenylamine (1 g.), acetic anhydride (6 c.c.), and fused sodium acetate (2 g.) was refluxed for 3 hours and then poured into water. After the excess of acetic anhydride had hydrolysed, the precipitated acetyl compound was removed; it crystallised from ethanol (charcoal) in fine colourless needles, m. p. 181° (Found: N, 14·2. $C_{14}H_{11}O_5N_3$ requires N, 14·0%). N-*Benzoyl*-3 : 3′-*dinitrodiphenylamine* was formed when a mixture of 3 : 3′-dinitrodiphenylamine (13 g.), benzoyl chloride (15 c.c.), and pyridine (20 c.c.) was refluxed for 3 hours, cooled, and treated with cold 3% aqueous hydrochloric acid until the product had solidified; it was then removed, treated with hot aqueous sodium hydrogen carbonate, and washed with water; it recrystallised from ethanol (charcoal) in minute colourless needles, m. p. 145° (Found: N, 11·9. $C_{19}H_{13}O_5N_3$ requires N, 11·6%), which were readily soluble in the usual organic solvents except ligroin and readily hydrolysed by hot acids and alkalis; the ethanol solution afforded a yellow colour when treated with aqueous sodium hydroxide.

Neutral Reduction of N-*Benzoyl*-3 : 3′-*dinitrodiphenylamine.*—A mixture of the compound (7·2 g.)

with iron powder (26 g., pin dust), ferrous sulphate (2·6 g.), and water (150 c.c.) was refluxed for 6 hours, cooled, and filtered, the residue was extracted thrice with ethanol (50 c.c. per time), and the ethanol was removed from the filtered extract; the crude *N-benzoyl-3 : 3′-diaminodiphenylamine* (5·9 g., 98% yield) separated from ethanol (charcoal) in colourless plates, m. p. 205° (Found : N, 13·9. $C_{19}H_{17}ON_3$ requires N, 13·9%), which were readily soluble in the usual organic solvents and in dilute mineral acids, slightly soluble in hot water and in ligroin. This compound was readily hydrolysed with 10% aqueous hydrochloric acid, and an ether extract of the liquor afforded benzoic acid, m. p. and mixed m. p. with an authentic specimen 121°; an ether extract of the liquor after it had been made alkaline gave 3 : 3′-diaminodiphenylamine, m. p. and mixed m. p. with an authentic specimen 95°.

N-Benzoyldiphenylamine-3 : 3′-bisazo-β-naphthol was obtained when a solution of *N*-benzoyl-3 : 3′-diaminodiphenylamine (0·5 g.) in 3% hydrochloric acid (10 c.c.) was diazotised by addition below 5° of a solution of sodium nitrite (0·3 g.) in the minimum amount of water, and the clear solution stirred into 10% aqueous sodium hydroxide (10 c.c.) containing β-naphthol (1 g.). After 30 minutes the precipitate was coagulated by heat, removed, washed with hot water, and then dissolved in hot glacial acetic acid (charcoal), from which it separated on cooling in red microcrystals, m. p. 303° (Found : N, 11·7. $C_{39}H_{27}O_2N_5$ requires N, 11·4%), which gave a magenta-coloured solution in concentrated sulphuric acid, turning to pink on dilution.

3 : 3′-Dinitrodiphenylamine was reduced by refluxing it (13 g.) for 3 hours with iron powder (50 g.), ferrous sulphate (2 g.), and water (50 c.c.), after which charcoal was added and the boiling continued for a further 30 minutes. The mixture was filtered, while boiling, on to ice (100 g.), placed in the filtration flask, and the residue washed with boiling water (50 c.c.). On cooling, 3 : 3′-diaminodiphenylamine (9·2 g., 90%) separated in colourless hexagonal plates which on recrystallisation from hot water had m. p. 95° (Albert and Linnell, *loc. cit.*, give m. p. 95°) (Found : N, 21·3. Calc. for $C_{12}H_{13}N_3$: N, 21·1%) and were stable in air. The compound is readily soluble in the usual organic solvents, dilute acids, and hot water. When this amine (1 g.) was dissolved in ether (50 c.c.) and the solution stirred with acetic anhydride (2 c.c.), opalescence occurred after a few minutes, and addition of water followed by careful introduction of steam caused separation of 3 : 3′-diacetamidodiphenylamine which crystallised from ether in colourless micro-crystals, m. p. 211° (Albert and Linnell, *loc. cit.*, give m. p. 211°) (Found : N, 15·0. Calc. for $C_{16}H_{17}O_2N_3$: N, 14·8%), which form tar very readily and cannot be obtained from solutions which have been previously overheated.

3 : 3′-*Di*-(*ω-carboxymethylamino*)*diphenylamine*.—A mixture of 3 : 3′-diaminodiphenylamine (2·1 g., 0·01 g.-mol.), chloroacetic acid (1·9 g., 0·02 g.-mol.), sodium carbonate (1·06 g.), and water (1·5 c.c.) was heated on the water-bath for 4 hours, cooled, and made alkaline; complete dissolution then occurred. The filtered solution was acidified with dilute hydrochloric acid, and the yellow precipitate of the *diglycino*-compound (2 g., 66% yield) collected and crystallised from hot water; it separated in yellow micro-crystals which on heating became chocolate-brown at 100°, sintered at 100°, and decomposed at *ca.* 350° (Found : N, 13·5. $C_{16}H_{17}O_4N_3$ requires N, 13·3%), and were readily soluble in cold dilute alkali, less so in cold dilute acids, but more soluble on heating, also soluble in cold pyridine, hot glacial acetic acid, and ethanol, but insoluble in chloroform, toluene, ether, and ligroin. The solutions were yellow when dilute but brown when more concentrated, and exhibited a slight green fluorescence.

The authors thank the Huddersfield Education Authority for a Research Scholarship to one of them (D. P. D.), Imperial Chemical Industries Limited (Dyestuffs Division) for gifts of chemicals, and Mr. Frank Hobson for micro-analyses.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, July 10th*, 1947.]

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197. *The Nitration of Benz-1-thia-2 : 3-diazole and the Synthesis of 7-Nitro-, 5-Methyl-, and 7-Nitro-5-methyl-benz-1-thia-2 : 3-diazole, with Improved Preparations of 1-Chloro-2 : 6-dinitrobenzene and 2-Chloro-3-nitroaniline.*

By HERBERT H. HODGSON and DOUGLAS P. DODGSON.

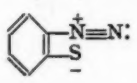
The synthesis of 7-nitrobenz-1-thia-2 : 3-diazole from 2-chloro-3-nitroaniline by thiolation and subsequent treatment with nitrous acid, has enabled the mononitration products of benz-1-thia-2 : 3-diazole to be identified as the 4- and the 7-nitro-isomeride. The 5-methyl and 7-nitro-5-methyl compounds have been prepared from 4-chloro-3-nitrotoluene and 4-chloro-5-nitro-*m*-toluidine respectively as initial substances. Improved preparations of 1-chloro-2 : 6-dinitrobenzene and 2-chloro-3-nitroaniline are described.

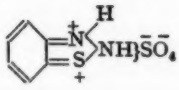
THE nitration of benz-1-thia-2 : 3-diazole had been carried out by Fries and Reitz (*Annalen*, 1936, **527**, 38), who isolated two compounds of m. p. 95° and 104°, the former predominating. Since 5- and 6-nitrobenz-1-thia-2 : 3-diazoles were known already, Fries and Reitz assumed the product of m. p. 95° to be the 4-isomeride, but they neither established its identity nor gave any opinion as to the structure of the product of m. p. 104°, since an attempted synthesis of 4-nitrobenz-1-thia-2 : 3-diazole from 2-nitrothioacetanilide was unsuccessful. In the present work, 7-*nitrobenz*-1-*thia*-2 : 3-*diazole* has been synthesised by thiolation of 2-chloro-3-nitroaniline

with aqueous sodium sulphide in the presence of sodium hydrogen carbonate (cf. Hodgson and Birtwell, *J.*, 1944, 75), and the resulting 2-nitro-6-aminothiophenol converted by nitrous acid into 7-nitrobenz-1-thia-2 : 3-diazole which had m. p. 105°, and was identical with the product prepared according to Fries and Reitz's directions (*loc. cit.*). The compound of m. p. 95° must therefore, by exclusion, have been the 4-nitrobenz-1-thia-2 : 3-diazole, thus confirming their assumption that nitration of benz-1-thia-2 : 3-diazole occurs in the 4- and 7-positions.

The resistance of the thiadiazole ring towards concentrated nitric acid affords further evidence of the great stability of the $-\dot{N}=\dot{N}-S-$ grouping, and the solubility of such compounds in strong mineral acids, thereby indicating the salt-forming character of the group, must be ascribed to the lone pairs of electrons present. The possibility of a diazonium structure (I) being produced by the acid would follow on analogy with the diazo-oxides, but this is ruled out by the fact that 5-aminobenz-1-thia-2 : 3-diazole on diazotisation followed by the Sandmeyer reaction gives a 5-halogenobenz-1-thia-2 : 3-diazole (cf. Hodgson and Dodgson, this vol., p. 870) and not a dihalogeno-compound such as a bis-diazonium compound would be expected to provide.

Benz-1-thia-2 : 3-diazole in many respects is similar to naphthalene but differs from it in the severe conditions required for its nitration and also in the intense violet-blue colour given with concentrated sulphuric acid; the latter suggests salt-formation of the type (II).

(I.) 

 (II.)

The preparation of 1-chloro-2 : 6-dinitrobenzene was necessary for the synthesis of 7-nitrobenz-1-thia-2 : 3-diazole, and for this purpose Borsche and Rantscheff's method (*Annalen*, 1911, **279**, 152) was modified by the use of potassium xanthate in place of sodium acetoacetic ester, whereby a pure product was obtained by a simplified technique, since the xanthate only reacts with the 1-chloro-2 : 4-dinitrobenzene in the mixture of the 2 : 4- and 2 : 6-isomerides obtained in the nitration of 1-chloro-2-nitrobenzene. Alternatively, the 1-chloro-2 : 6-dinitrobenzene was obtained from 2 : 6-dinitrosulphanilic acid (Lindemann and Wessel, *Ber.*, 1925, **58**, 1221) by desulphonation, diazotisation (Hodgson and Walker, *J.*, 1933, 1620), and finally the Sandmeyer reaction.

Reduction of 1-chloro-2 : 6-dinitrobenzene was readily effected by stannous chloride in glacial acetic acid solution to give 2-chloro-3-nitroaniline.

2 : 2′-Dinitro-4 : 4′-dimethyldiphenyl disulphide was prepared in 48% yield by the action of sodium disulphide on 4-chloro-3-nitrotoluene, and converted by reduction into 3-nitrothio-*p*-cresol, which, on diazotisation, afforded *5-methylbenz-1-thia-2 : 3-diazole*. This compound somewhat resembled the parent substance in giving a blue colour with concentrated sulphuric acid. *7-Nitro-5-methylbenz-1-thia-2 : 3-diazole* has likewise been obtained from 4-chloro-3 : 5-dinitrotoluene by a similar process to that used for the synthesis of 7-nitrobenz-1-thia-2 : 3-diazole, *viz.*, reduction to *4-chloro-5-nitro*-m-*toluidine* with subsequent thiolation and diazotisation.

Unlike 2-chloro-5-nitroaniline, both 2-chloro-3-nitroaniline and 4-chloro-5-nitro-*m*-toluidine yield a considerable amount of brown by-product on thiolation; this appears to indicate some reduction of the second nitro-group, since diazotisation produces Bismarck-brown-like products.

Whereas 2-chloro-5-nitroaniline readily thiolates and on diazotisation gives a cream-coloured product which is fairly pure (Hodgson and Dodgson, *loc. cit.*), a similar treatment of 2-chloro-3-nitroaniline afforded a much browner product from which the thiadiazole had to be purified by sublimation. Working with the similar compound, 4-chloro-5-nitro-*m*-toluidine, the brown product and the thiadiazole could be separated by extraction of the latter with hot 20% hydrochloric acid. It is suggested that in the cases of brown product formation, the second nitro-group which is also adjacent to the chlorine has been partially reduced by the sulphide with some resulting diamine, which, in the subsequent diazotisation, has yielded Bismarck-brown-like compounds.

In attempts to find a rapid method for the preparation of 1-chloro-2 : 6-dinitrobenzene, the mixture of 1-chloro-2 : 4-dinitro- and 1-chloro-2 : 6-dinitro-benzenes, obtained by the nitration of 1-chloro-2-nitrobenzene, was first treated with potassium phthalimide in boiling ethanol without result; when the reactants were fused together some reaction occurred at about 120° but was incomplete and could not be used for the separation (cf. Schmidt, *Ber.*, 1889, **22**, 3249, for the reaction of picryl chloride with potassium phthalimide which takes place at 70°). In

the case of the reaction with potassium xanthate above, only mixtures of m. p. <43° could be used, otherwise no 1-chloro-2 : 6-dinitrobenzene could be isolated.

Experimental.

Preparation of Benz-1-thia-2 : 3-diazole.—A mixture of aniline (93 g., 1 g.-mol.) and sulphur (64 g., 2 g.-mols.) was refluxed at 180—190° for 12 hours, and the cooled melt extracted with 2% aqueous hydrochloric acid to remove unchanged aniline. The residue, consisting mainly of *oo'*-dithioaniline, was suspended in hot 15% aqueous hydrochloric acid (500 c.c.) and saturated with hydrogen sulphide, after which the stirred mixture was cooled below 5°, treated with sodium nitrite (70 g.) dissolved in water (250 c.c.), kept for one hour, and then steam distilled; benz-1-thia-2 : 3-diazole passed over and was purified by steam distillation from 5% aqueous sodium hydroxide. Yield, 27 g. (20%); m. p. 35° (Jacobson, *Annalen*, 1893, **277**, 209, gives m. p. 35°) (Found : S, 23·6. Calc. for $C_6H_4N_2S$: S, 23·5%).

Nitration of Benz-1-thia-2 : 3-diazole.—The violet solution of the compound (13·6 g.) in sulphuric acid (60 c.c., *d* 1·84) was stirred gradually at room temperature with finely powdered potassium nitrate (12 g.); the colour changed to red and thence to pale yellow-brown, accompanied by a temperature rise of *ca.* 16° (precipitation experiments at this point indicated that nitration had not taken place). On being heated gradually to 100°, the solution turned brown, and was then cooled, poured on ice, and the precipitated mixture of the 4- and 7-nitrobenzthiadiazoles filtered off. This mixture contained no steam-volatile constituent, and recrystallisation from methanol and subsequently from toluene afforded needles of m. p. 70—80° raised to 87—92° when sublimed under reduced pressure at 140°. Fractional crystallisation of the sublimate from ethanol, and recrystallisation of the fractions, gave products of m. p. 95° (Found : S, 18·0. Calc. for $C_6H_3O_2N_3S$: S, 17·7%) and 105° (Found : S, 18%), respectively; Fries and Reitz (*loc. cit.*) give m. p.s 95° and 104°.

Nitration of 1-Chloro-2-nitrobenzene.—Nitric acid (31·5 g., *d* 1·4) was stirred gradually into a solution of 1-chloro-2-nitrobenzene (31·5 g.) in sulphuric acid (130 c.c., *d* 1·84), and the reaction mixture heated on the water-bath to 100°, cooled to room temperature, poured on ice, and the precipitated 1-chloro-2 : 4- and -2 : 6-dinitrobenzene removed as a white solid, washed with water, and dried. Slow crystallisation from their solution in ethanol afforded fractions whose m. p.s varied from 38° to 50°, the lower ones consisting mainly of needles and the higher of rhombic plates which were almost pure 1-chloro-2 : 4-dinitrobenzene. The former fractions containing the highest proportion of 1-chloro-2 : 6-dinitrobenzene were worked up as follows : A fraction (10 g.), of m. p. 43° or less, was dissolved in ethanol (100 c.c.), treated with potassium xanthate (4 g.), and the volume concentrated to 30 c.c. Ether (50 c.c.) was added, and the red colour, which was produced initially, had by this time given place to a yellow precipitate which consisted mainly of the monosulphides from the chlorodinitrobenzenes; it was filtered off, washed with ether, and the combined ethereal filtrates extracted with 2% aqueous sodium hydroxide, followed by water until the washings were colourless. The ether was allowed to evaporate gradually; 1-chloro-2 : 6-dinitrobenzene crystallised out (aided by scratching) and was filtered off and washed with ether–ligroin (1 : 1) to remove the xanthic ester also produced and finally with ligroin; yield, 1·7 g. On crystallisation from methanol, it had m. p. 88° (Borsche and Rantscheff, *Annalen*, 1914, **406**, 101, give m. p. 88°) (Found : Cl, 17·2. Calc. for $C_6H_3O_4N_2Cl$: Cl, 17·5%). Attempts to separate 1-chloro-2 : 6-dinitrobenzene from the crude mixture itself did not succeed, and it became necessary to fractionate as above; similarly, an attempted separation by reaction with potassium phthalimide also failed, since on using 80% of the theoretical amount of this reagent ,no reaction took place even after refluxing in ethanol for 6 hours, while fusion of the reactants at 120° only brought about a partial reaction, in contrast to the ready reaction of picryl chloride with potassium phthalimide (cf. Schmidt, *Ber.*, 1889, **22**, 3249) which ensues at 70°.

Alternative Preparation of 1-Chloro-2 : 6-dinitrobenzene.—4-Chloro-3 : 5-dinitrobenzenesulphonic acid was obtained when a mixture of chlorobenzene (45 c.c.), 20% oleum (90 c.c.), sulphuric acid (830 c.c., *d* 1·84), and potassium nitrate (225 g.) was heated on a boiling water-bath for 16 hours, cooled, and poured on ice (5 kg.). The product was filtered off, washed with ether (50 c.c.) to remove chlorodinitrobenzenes, and crystallised from hot water, forming colourless plates, m.p. 293° (Ullmann and Kuhn, *Annalen*, 1909, **366**, 102, give m. p. 293°) (Found : S, 11·5. Calc. for $C_6H_2O_7N_2ClS$: S, 11·3%). The above sulphonic acid (20 g.) was suspended in ammonia (50 c.c., *d* 0·88), the mixture heated to boiling under reflux, cooled, and the yellow 2 : 6-dinitrosulphanilic acid which had been formed was filtered off, and washed with water (20 c.c.), and then crystallised from hot water in yellow needles which exploded at 360° (Found : S, 12·2. Calc. for $C_6H_3O_7N_3S$: S, 12·2%. Desulphonation was effected when this sulphonic acid was refluxed for 3 hours with sulphuric acid (120 c.c., *d* 1·84) and water (80 c.c.); on cooling, yellow plates (5 g.) of 2 : 6-dinitroaniline separated which when recrystallised from methanol had m. p. 139° (Welsh, *J. Amer. Chem. Soc.*, 1941, **63**, 3276, gives m. p. 139°) (Found : N, 23·2. Calc. for $C_6H_5O_4N_3$: N, 22·9%). A solution of this amine (4·5 g.) in sulphuric acid (20 c.c., *d* 1·84) was stirred into one of sodium nitrite (2 g.) in sulphuric acid (10 c.c., *d* 1·84), and glacial acetic acid (30 c.c.) was then added with stirring; after 30 minutes, the mixture was poured into a cold solution of cuprous chloride (10 g.) in hydrochloric acid (100 c.c., *d* 1·18) and kept until evolution of nitrogen had ceased. On dilution with water (50 c.c.), crude 1-chloro-2 : 6-dinitrobenzene separated and was filtered off, extracted with ether (100 c.c.), and the filtered extract washed first with 2% aqueous sodium hydroxide until the washings were colourless, then with water; finally the ether was allowed to evaporate gradually, whereupon 1-chloro-2 : 6-dinitrobenzene separated (3·5 g., 70% yield) and was recrystallised from methanol; m. p. 88°.

Reduction of 1-Chloro-2 : 6-dinitrobenzene.—Reduction of this compound (2·025 g.) to 2-chloro-3-nitroaniline was effected by dissolving it in glacial acetic acid (4 c.c.) and treating it with crystallised stannous chloride (6·8 g.) added in small portions to the hot solution. After 5 mins.' refluxing, water (20 c.c.) was added, followed by 20% aqueous sodium hydroxide (30 c.c.), and the mixture was steam-distilled.

The distillate (3 l.) was cooled in ice, yellow needles of 2-chloro-3-nitroaniline (0·9 g., 53% yield) separating, a further 0·2 g. being obtained on concentration of the filtrate to 100 c.c.; it recrystallised from methanol in yellow needles, m. p. 96° (Wallach and Wibaut, *Rec. Trav. chim.*, 1936, **55**, 1075, give m. p. 95—96°) (Found : Cl, 20·9. Calc. for $C_6H_5O_2N_2Cl$: Cl, 20·6%).

Synthesis of 7-Nitrobenz-1-thia-2 : 3-diazole.—A solution of 2-chloro-3-nitroaniline (1·725 g.) in ethanol (25 c.c.) was treated gradually with one of crystalline sodium sulphide (3·6 g.) and sodium hydrogen carbonate (1·26 g.) in water (10 c.c.). The mixture was then heated on the water-bath for 2 hours, cooled, and water (65 c.c.) containing 20% aqueous sodium hydroxide (1 c.c.) added; the solution was then cooled in ice, filtered, sodium nitrite (1 g.) dissolved in it, and the whole stirred into sulphuric acid (25 c.c., *d* 1·84) mixed with ice (25 g.). After one hour, the brown precipitate of *7-nitrobenz-1-thia-2 : 3-diazole* (0·4 g., 22% yield) was collected and purified by sublimation under reduced pressure; subsequent recrystallisation from methanol gave crystals with m. p. and mixed m. p. with a sample of Fries and Reitz's unidentified nitration compound, 105°; cooled and remelted, m. p. 105° (Found : N, 13·4. $C_6H_3O_2N_3S$ requires N, 13·2%).

Synthesis of 5-Methylbenz-1-thia-2 : 3-diazole.—2 : 2′-Dinitro-4′-dimethyldiphenyl disulphide was obtained when a solution of 4-chloro-3-nitrotoluene (13·72 g.) in ethanol (200 c.c.) was treated with one of sodium sulphide nonahydrate (9·6 g.) and sulphur (1·28 g.) in water (25 c.c.) and the mixture refluxed for 3 hours, after which the yellow disulphide (6·4 g., 48% yield) was filtered off and crystallised from 80% aqueous acetic acid (charcoal), forming yellow needles, m. p. 176° (Zincke and Röse, *Annalen*, 1914, **405**, 108, give m. p. 176°) (Found : S, 19·4. Calc. for $C_{14}H_{12}O_4N_2S_2$: S, 19·1%). This disulphide (3·36 g.) was suspended in 90% aqueous acetic acid (100 c.c.) with zinc dust (7 g.), and the mixture heated under reflux for one hour, filtered hot, the filtrate cooled to 10°, then stirred into a solution of sodium nitrite (1·5 g.) in sulphuric acid (10 c.c., *d* 1·84). The mixture was then poured on ice (100 g.), kept for one hour, made alkaline, and steam-distilled, whereupon the *5-methylbenz-1-thia-2 : 3-diazole* came over as an oil which solidified on cooling; it was dissolved in boiling methanol (charcoal) from which it separated, when the methanol was gradually evaporated under reduced pressure, in clusters of small rods, m. p. 26° (Found : N, 18·9. $C_7H_6N_2S$ requires N, 18·7%), which gave a grey-blue solution in concentrated sulphuric acid, from which the thiadiazole was precipitated unchanged on dilution with water.

Synthesis of 7-Nitro-5-methylbenz-1-thia-2 : 3-diazole.—A solution of sodium nitrite (10 g.) in sulphuric acid (70 c.c., *d* 1·84) was stirred into one of 3 : 5-dinitro-*p*-toluidine (19·7 g.) in sulphuric acid (30 c.c., *d* 1·84) followed by glacial acetic acid (150 c.c.), the temperature being kept below 30° and the stirring continued for one hour. The mixture was then stirred into a solution of cuprous chloride (40 g.) in hydrochloric acid (150 c.c., *d* 1·18), kept until evolution of nitrogen had ceased (30 mins.), and poured on ice (1 kg.); the precipitate was filtered off, washed with water at the pump, extracted twice with boiling ethanol (2 × 100 c.c.), the extract filtered, the filtrate poured into ice–water (1 l.), aqueous 4% sodium hydroxide added (100 c.c.), and the precipitate (17 g., 78·5% yield) of crude 4-chloro-3 : 5-dinitrotoluene crystallised from ethanol in yellow needles, m. p. 116° (Borsche and Fiedler, *Ber.*, 1913, **46**, 2121, give m. p. 115—116°). A solution of this compound (21·65 g.) in hot glacial acetic (100 c.c.) was treated with powdered crystalline stannous chloride (67·8 g.) added in portions just sufficient to maintain ebullition, and when the addition was complete (2—3 mins.) the mixture was boiled for a further 5 minutes, diluted with water (100 c.c.), and poured into 10% sodium hydroxide in ice–water (1200 g., 1 : 1); when the precipitate had coagulated, it was filtered off, washed with water, dissolved in hot 20% hydrochloric acid (150 c.c.), the solution filtered hot, and the filtrate cooled, and neutralised with ammonia; the *4-chloro-5-nitro-3-aminotoluene* (*4-chloro-5-nitro-m-toluidine*) was filtered off and steam-distilled, and the distillate cooled to 0°, affording the pure product, which crystallised from methanol in yellow needles, m. p. 95° (Found : N, 15·3. $C_7H_7O_2N_2Cl$ requires N, 15·0%). *4-Chloro-5-nitro-3-aceto-m-toluidide*, prepared by the usual acetylation procedure, crystallised from ethanol in pale cream needles, m. p. 147° (Found : N, 12·5. $C_9H_9O_3N_2Cl$ requires N, 12·25%).

Thiolation of 4-Chloro-5-nitro-m-toluidine.—A mixture of a solution of the compound (9·325 g.) in ethanol (125 c.c.) with one of sodium sulphide nonahydrate (18 g.) and sodium hydrogen carbonate (6·3 g.) in water (50 c.c.), was refluxed on the water-bath for an hour, 20% aqueous sodium hydroxide (10 c.c.) added, and the whole poured into ice–water (400 c.c.), filtered, and the residue washed with a little water and dried to give unchanged material (2·9 g., 31% of that taken). Sodium nitrite (4 g.) was dissolved in the filtrate, which was then stirred at 0° into sulphuric acid (12·5 c.c., *d* 1·84) which had been diluted with ice–water (125 c.c.). After one hour, the crude brown product was extracted thrice with boiling 20% aqueous hydrochloric acid (3 × 50 c.c.), and from the solution the *7-nitro-5-methylbenz-1-thia-2 : 3-diazole* was precipitated by addition of ice–water (150 c.c.) (yield, 0·5 g., m. p. 130—150°); it sublimed in minute yellow needles, m. p. 149° (Found : N, 21·8. $C_7H_5O_2N_3S$ requires N, 21·5%), which were dissolved in concentrated sulphuric acid to give a colourless solution from which the thiadiazole was precipitated unchanged on dilution with water. The residue (3·2 g.) from the above hydrochloric acid extraction was readily soluble in ethanol, but attempts at identification were unsuccessful.

The authors thank the Huddersfield Education Authority for a Research Scholarship to one of them (D. P. D.), Imperial Chemical Industries Limited (Dyestuffs Division) for gifts of chemicals, and Mr. Frank Hobson for microanalyses.

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198. *Esters Containing Phosphorus. Part VI. Preparation of Esters of Fluorophosphonic Acid by Means of Phosphorus Oxydichlorofluoride.*

By N. B. Chapman and B. C. Saunders.

An account is given of the synthesis of esters of fluorophosphonic acid by the action of the appropriate alcohol on phosphorus oxydichlorofluoride, and for this purpose a convenient preparation of the latter compound is given. In particular the preparation and properties of the highly toxic *di*cyclo*hexyl fluorophosphonate* are described.

Phosphorus oxydichlorofluoride also reacts with ethylthiol in the presence of a tertiary base producing *diethyl fluorodithiophosphonate* which, in marked contrast to diethyl fluorophosphonate, is relatively non-toxic and devoid of miotic properties. Among other esters described is *di*-2-*fluoroethyl fluorophosphonate* which possesses interesting pharmacological properties.

In a Report to the Ministry of Supply (Feb. 27, 1942) a method was proposed for synthesising esters of fluorophosphonic acid by the reaction between phosphorus oxychloride and the appropriate alcohol:

$$O{:}PCl_2F + 2ROH = O{:}PF(OR)_2 + 2HCl \qquad (I.)$$

The reaction depended upon the marked difference in reactivity between the chlorine atoms and the fluorine atom in phosphorus oxydichlorofluoride. In general the reaction with alcohols was clear cut, and most of the fluorophosphonic esters were obtained in excellent yield and uncontaminated with the phosphoric triester. For example, when ethyl alcohol and phosphorus oxydichlorofluoride were allowed to react in the cold, diethyl fluorophosphonate (I, R = Et) was obtained in 93% yield. No tertiary base was necessary to remove the hydrogen chloride produced in the reaction. The general process was patented during the war (B.P., Ministry of Supply, McCombie, Saunders, Chapman, and Heap, April 17th, 1944).

The method depended upon the availability of phosphorus oxydichlorofluoride, a compound described by Booth and Dutton (*J. Amer. Chem. Soc.*, 1939, **61**, 2937) who devised an elaborate apparatus for the preparation of the compound in a pure condition for physicochemical measurements. We have modified their process to suit the particular needs of this work. The " generator " which we developed for this step-wise fluorination of phosphorus oxytrichloride by antimony trifluoride (and pentachloride as catalyst) is shown in the diagram. Full details of its construction and maintenance are given on p. 1011. On a kilogram scale the yield of pure phosphorus oxydichlorofluoride was *ca.* 20%.

In addition to diethyl fluorophosphonate, *di*-n-*propyl* and di*iso*propyl fluorophosphonate were prepared by the action of phosphorus oxydichlorofluoride on *n*-propyl and *iso*propyl alcohol respectively. The *n*-ester was less toxic and possessed only feeble miotic action compared with the ethyl and the *iso*propyl ester, the order of potency being $Pr^{\beta} > Et > Pr$. The ethyl and *iso*propyl esters were identical with the compounds obtained by the " hydrogen phosphate " method described by Saunders and Stacey (Part IV, this vol., p. 695).

In order to determine whether other secondary alcohols would give fluorophosphonic esters of high potency, *di*cyclo*hexyl fluorophosphonate* (II) was prepared by the action of phosphorus oxydichlorofluoride on *cyclo*hexanol. In this preparation it was essential to remove carefully all the hydrogen chloride before distillation, otherwise decomposition took place. The compound was a colourless, mobile liquid, b. p. 116°/0·3 mm., insoluble in water, and formed a " persistent gas ". It was extremely toxic (Report from Prof. Adrian to Ministry of Supply, Jan. 7th, 1943; and Report No. 9 on Fluorophosphonates by McCombie and Saunders, April 10th, 1943); at a nominal concentration of 1 : 12,500, the following died after a 10-minute exposure: 3/3 rabbits, 3/4 guinea-pigs, 6/6 rats, 10/10 mice. The pupils of the animals' eyes contracted to pin-point size and there were the usual " fluorophosphonate-like " convulsions before death. More precise toxicity experiments showed that the approximate L.C. 50 (see Part IV) for a 10-minute exposure for mice, rats, and rabbits was 0·11—0·14 mg./l. (guinea-pigs appeared to be more resistant). This means that di*cyclo*hexyl fluorophosphonate was more toxic than di*iso*propyl fluorophosphonate (Part IV, *loc. cit.*).

Whereas diethyl fluorophosphonate was hydrolysed in aqueous solution in about 4 hours, the di*iso*propyl ester required some 72 hours for complete hydrolysis, and could be steam-distilled. Di*cyclo*hexyl fluorophosphonate was very stable, and vigorous shaking with water did not produce any appreciable hydrolysis. It was hydrolysed by boiling water only after several hours. When stirred vigorously with 2% sodium hydroxide solution at 28·5°,

the time taken to bring about hydrolysis according to the equation $(C_6H_{10}O)_2POF + 2NaOH = (C_6H_{10}O)_2PO{\cdot}ONa + NaF + H_2O$ was of the order of 90 minutes. On prolonged shaking, hydrolysis proceeded beyond the stage represented above. With occasional shaking (*i.e.*, under conditions comparable with those employed in decontamination) in the presence of 2% sodium hydroxide hydroxide solution at 20°, hydrolysis proceeded to an extent of only 64% after 220 minutes.

In view of the greater toxicity often observed with derivatives of *o*-cresol compared with derivatives of phenol itself, it seemed worth while to prepare *di*-(o-*methyl*cyclo*hexyl*) *fluorophosphonate*. At a concentration of 0·65 mg./l., only 3 out of a batch of 23 animals (rabbits, guinea-pigs, rats, and mice) were killed. The animals which died (the rabbits) exhibited muscular twitchings, but miosis was not very marked. The compound was therefore much less toxic than the corresponding unsubstituted di*cyclo*hexyl fluorophosphonate.

Di-2-chloroethyl fluorophosphonate was obtained from phosphorus oxydichlorofluoride and chlorohydrin, and in a chamber at a concentration of 1 : 10,000 (1·0 mg./l.) caused some irritation of the eyes and nose of the animals. After exposure, the irritant effects rapidly subsided and no other effects were observed. A small number of animals died as follows: 0/3 rabbits, 1/4 guinea-pigs (12 hours), 1/6 rats (4½ days), 3/10 mice (12 hours, 5½ days, 7½ days). The compound was therefore relatively non-toxic. Elsewhere it is recorded that 2-fluoroethyl alcohol is highly toxic (McCombie and Saunders, *Nature*, **1946**, **158**, 382), and that 2-fluoroethyl fluoroacetate is markedly more toxic than either fluoroethyl alcohol or fluoroacetic acid (weight for weight). In view of this enhanced toxicity it seemed desirable to investigate the effect of introducing the 2-fluoroethyl group into the fluorophosphonate molecule. Accordingly, *di-(2-fluoroethyl) fluorophosphonate* (III) was prepared from phosphorus oxydichlorofluoride and fluoroethyl alcohol. The compound, a mobile liquid, exhibited lower toxicity than either fluoroethyl alcohol or diethyl fluorophosphonate. At a concentration of 0·5 mg./l. (10 mins.' exposure) it did, however, produce a remarkable effect on rats. An hour or so after exposure two out of six rats became extremely violent, rushed about the cage, and exhibited a type of hyperactivity which caused them to bite the legs of their companions. The two rats died of convulsions of an unusual type. The phenomenon was repeatable. The compound also caused miosis.

$O{:}PF(O{\cdot}C_6H_{11})_2$	$O{:}PF(O{\cdot}CH_2{\cdot}CH_2F)_2$	$O{:}PF(SEt)_2$
(II.)	(III.)	(IV.)

Diphenyl fluorophosphonate was prepared in 60% yield by the action of phosphorus oxydichlorofluoride on phenol in the presence of dimethylaniline to take up the hydrogen chloride formed. Gottlieb (*J. Amer. Chem. Soc.*, **1936**, **58**, 532) claimed to have prepared this compound in 7% yield by the action of potassium fluoride on the corresponding chlorophosphonate. His compound was rapidly decomposed by water, whereas ours was stable (in accordance with expectation); furthermore, he gave no fluorine analysis. It is doubtful therefore whether Gottlieb obtained an authentic specimen of diphenyl fluorophosponate. We showed that diphenyl fluorophosphonate was non-toxic and possessed negligible miotic action.

There appeared to be no appreciable reaction between ethylthiol and phosphorus oxydichlorofluoride, whereas the sodium thioethoxide reacted with all three halogen atoms producing triethyl trithiophosphate, $O{:}P(SEt)_3$. It was found, however, that if dimethylaniline were used as the condensing agent then the two chlorine atoms were removed while the fluorine atom remained unaffected. *Diethyl fluorodithiophosphonate* (IV) thus obtained was a liquid, and unlike the corresponding oxygen analogue (I, R = Et) was non-toxic and devoid of miotic properties.

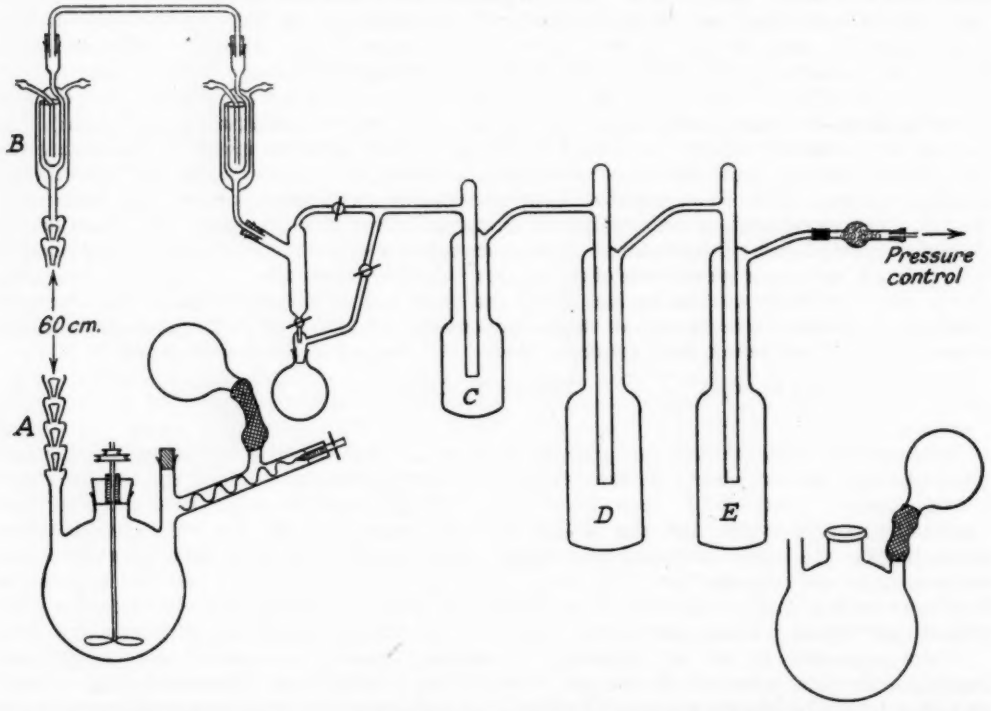
Experimental.

Phosphorus Oxydichlorofluoride.—Apparatus. The generator employed is shown in the diagram. Important points are: (1) The column *A* was efficient and designed so that throttling was avoided; it was at least 2 feet long and surmounted by a reflux double-surface water-condenser *B*. (2) A Perkin triangle (air-cooled), inserted between the down-condenser and the traps, enabled any phosphorus oxychloride which distilled to be removed (usually only a small quantity condensed in the triangle during a normal run). (3) It was convenient to have three traps, *viz.*, *C*, ice–salt; *D*, acetone–carbon dioxide; *E*, liquid air. (4) The intermittent addition of the solid antimony trifluoride presented a problem. The mechanical " solid " feed shown in the diagram proved fairly satisfactory over short periods of working. There was a tendency, however, for the wire screw-feed to become jammed as the antimony fluoride became damp during the experiment. A less elegant, but more reliable device for long periods of working is shown in the small diagram. It consists of a round-bottomed flask attached directly to the reaction vessel by means of a flexible, special quality, corrosion-resisting, rubber hose. (5) The stirrer was made of stainless steel with strengthened paddles; the stirrer gland was packed freshly before each run, and was filled as full as possible. (6) Silicone grease was used on all joints. Ground-glass joints were used

where possible, but some rubber connexions (strong pressure tubing) were employed at certain points to provide flexibility. Considerable vibration was caused by vigorous stirring. The necessary reduced pressure (200 mm.) was maintained by a steel water-pump and moving-bell type manostat.

Procedure. Finely powdered antimony trifluoride (800 g.) was placed in the reservoir of the feed. Phosphorus oxychloride (2000 g.) and then antimony pentachloride (500 g.) were placed in the reaction vessel. The temperature of the bath was maintained, thermostatically, at 75° and the pressure kept at 190—200 mm., and the antimony trifluoride was then added slowly from the feed. The duration of addition varied from 2 to 6 hours, the slowest rate being the best. The distillates in the traps were united and fractionated. The distillate, up to b. p. 90°/760 mm., was collected and carefully refractionated, giving 360 g. (20%) of pure phosphorus oxydichlorofluoride, b. p. 54°.

In a smaller-scale experiment, the following quantities were used: Phosphorus oxychloride (500 g.), antimony trifluoride (200 g., added during 3—4 hours), antimony pentachloride (60 c.c.). After the conclusion of the experiment 137 g. of phosphorus oxychloride were recovered from the residue in the reaction-vessel by distillation up to 200° (at which antimony compounds began to come over), and 57 g. from the Perkin triangle and traps. The yield of oxydichlorofluoride was 90 g., *i.e.*, 20%, or 34% after allowance for the oxychloride recovered. When double the quantity of antimony trifluoride was used, there was no excess of phosphorus oxychloride left in the reaction vessel, but there was no increase



in the yield of oxydichlorofluoride: it appeared that the extra antimony trifluoride had converted the "excess" of phosphorus oxychloride into oxychlorodifluoride and oxytrifluoride.

Diethyl Fluorophosphonate.—Phosphorus oxydichlorofluoride (5·5 g.) was placed in a Claisen flask (possessing a fractionating column) and fitted with a calcium chloride tube. Ethyl alcohol (4 g., 10% excess) was slowly run in, the temperature not being allowed to rise above 5°. The hydrogen chloride was removed by suction at room temperature, and the residue carefully heated to remove excess of alcohol and hydrogen chloride. When the residue was distilled under reduced pressure, almost the entire liquid came over at 70—72°/18 mm.; yield, 5·8 g. (93%). The product contained fluorine and only traces of chloride. A second distillation at 70—72°/18 mm. gave a product completely free from chloride (Found: F, 12·2. Calc. for $C_4H_{10}O_3FP$: F, 12·17%) which was further characterised by its b. p., 171°/760 mm., and powerful miotic action. 1 Mol. of the compound required 2 mols. of sodium hydroxide (N/2 solution) for hydrolysis in the cold or on being gently heated under reflux for 30 minutes; this is in accordance with the equation $PO(OEt)_2F + 2NaOH = PO(OEt)_2ONa + NaF + H_2O$ (see Part IV).

Di-n-propyl Fluorophosphonate.—*n*-Propyl alcohol (20 g., 15% excess) was slowly run into phosphorus oxydichlorofluoride (20 g.). Heat was evolved during the reaction and the temperature was kept down to 5°. The mixture was set aside for several hours, and the excess of hydrogen chloride removed by drawing air through the liquid, which was then distilled. The fraction of b. p. 96—102°/20 mm. (25 g., 93%) was almost pure *di-n-propyl fluorophosphonate*. It was redistilled at 98—100°/20 mm. (Found: F, 10·28, 10·39. $C_6H_{14}O_3FP$ requires F, 10·32%).

Diisopropyl Fluorophosphonate.—Phosphorus oxydichlorofluoride (50 g.) was dissolved in dry ether

(100 c.c.), *iso*propyl alcohol (dried over calcium oxide; 50 g., 15% excess) in dry ether (100 c.c.) was added slowly with cooling, and the mixture kept for one hour. Dry ammonia was then passed through the liquid, with cooling. The liquid was then filtered, if necessary, and the excess of ammonia and ether taken off at room temperature. The residue was distilled, and the fraction, b. p. 37—47°/0·5 mm., collected. This redistilled at 84—85°/25 mm.; yield, 60 g. (45%) (Found: F, 10·1%).

Dicyclohexyl Fluorophosphonate.—Phosphorus oxydichlorofluoride (68·5 g., 0·5 mol.) was dissolved in dry ether (150 c.c.) and well cooled in ice–salt. *cyclo*Hexanol (100 g., 1·0 mol.) in dry ether (150 c.c.) was slowly dropped in and the mixture kept over-night. In order to remove hydrogen chloride, air (dried with H_2SO_4, NaOH, and P_2O_5) was drawn through the resultant liquid for about 5 hours. More dry ether was then added, and dry ammonia passed through the liquid until no more ammonium chloride was precipitated. The ammonium chloride was filtered off, and the filtrate kept over lead carbonate for some time, filtered, and the filtrate dried (Na_2SO_4). After distillation of the ether, the residue was distilled in a " semi-molecular " still, without air-leak, glass-wool being used to prevent splashing. The fraction of b. p. 90—96°/0·02 mm. was collected. The liquid could also be distilled at slightly higher pressures in an atmosphere of nitrogen. After the " initial " distillation the above precautions were usually not necessary for further distillations; yield, 126 g. (70%). *Dicyclohexyl fluorophosphonate* was a colourless, mobile liquid, insoluble in water (Found: F, 7·3, 6·9. $C_{12}H_{22}O_3FP$ requires F, 7·12%).

Notes on the preparation. (a) The *cyclo*hexanol was heated under reflux over quicklime and redistilled before use. (b) It was essential to remove all the hydrogen chloride produced in the reaction, otherwise decomposition was likely to take place during the final distillation. (c) Occasionally, specimens of di*cyclo*hexyl fluorophosphonate contain traces of ammonium chloride. This is readily removed by washing with water, drying (Na_2SO_4), and redistilling.

Hydrolysis of Dicyclohexyl Fluorophosphonate.—(a) *By water at* 20°. The ester (7·9 g.) was suspended in water, and the mixture made up to 250 ml. with distilled water and *vigorously stirred* in a thermostat at 20°, 25 ml. being withdrawn at intervals and titrated with standard alkali (about N/2), phenolphthalein being used as indicator. After 227 mins.' stirring the hydrolysis was only 0·025%, and this remained unchanged after a further 990 mins.' standing (this value is less than the experimental error of the determination). At the end of the experiment, the ester was separated, dried, and distilled, 5·8 g. being recovered; after allowance for losses, this confirms that the ester was practically unhydrolysed.

(b) *By approx.* N/2-*sodium hydroxide with vigorous stirring at* 28·5°. 8·85 G. of ester (0·0311 mol.) were stirred vigorously with 250 ml. of 0·642N-sodium hydroxide and 20-ml. samples withdrawn at intervals, and titrated against sulphuric acid (phenolphthalein as indicator):

Time, mins.	9	20	30	62·5	92	121·5	140
Hydrolysis, %	8·6	26·5	38·8	82·9	109·7	138·0	149·0

After a further 18 hours' standing, the hydrolysis was 153·1%.

(c) *By approx.* N/2-*sodium hydroxide with occasional shaking at* 20°. A similar experiment with 0·02934 mol. of ester and 250 ml. of 0·6415N-alkali gave the following results:

Time, mins.	27	59	100	151	230
Hydrolysis, %.	56·8	58·3	58·9	60·7	64·0

After a further 985 mins.' standing, the hydrolysis was 73·9% and the residue was undistillable at 0·3 mm. in nitrogen.

(d) *By approx.* N/2-50% *aqueous ethanolic sodium hydroxide at* 20°. 0·03481 Mol. of ester and 250 ml. of 0·5958N-alkali gave the following results:

Time, mins.	32·5	87	105	147	184	225	1215
Hydrolysis, %	18·7	114·0	111·2	109·7	111·6	114·0	111·6

The variations after 87 mins. are within the limits of experimental error.

Di-(o-*methyl*cyclo*hexyl*) *Fluorophosphonate.*—Phosphorus oxydichlorofluoride (34·25 g., 1 mol.) was dissolved in dry ether (100 c.c.) and cooled in ice and salt. *o*-Methyl*cyclo*hexanol (dried by refluxing over quicklime and distilling, 57 g., 2 mols.), dissolved in dry ether (100 c.c.), was added slowly to the oxydichlorofluoride solution, and the mixture kept overnight. Dry air was then passed through for 6—8 hours to remove hydrogen chloride, and then dry ammonia was passed in with ice-cooling to ensure complete removal of the residual hydrogen chloride. The ammonium chloride thus formed was filtered off, and the filtrate kept over lead carbonate, refiltered, and dried (Na_2SO_4 and kieselguhr). The ether was distilled off from the filtered solution, and the residue fractionated in a stream of nitrogen; b. p. 120°/0·1 mm., 137°/0·15 mm.; yield, 42 g. (60%). The b. p. was to some extent dependent upon the bath temperature, which was 190° for the second value. The *product* may have been a mixture of *cis*- and *trans*-isomers (Found: F, 6·53, 6·58. $C_{14}H_{26}O_3FP$ requires F, 6·51%).

Di-(2-*chloroethyl*) *Fluorophosphonate.*—Phosphorus oxydichlorofluoride (34·25 g.) was dissolved in dry ether (50 c.c.) and well cooled in ice-salt, and ethylene chlorohydrin (40·25 g.) in dry ether (50 c.c.) was slowly added. Hydrogen chloride was copiously evolved, the resultant liquid was set aside overnight, and dry air was then pulled through for at least 5 hours. The brown liquid so obtained was diluted with dry ether, and dry ammonia passed in until no more ammonium chloride was precipitated. The solid was filtered off, and the cloudy filtrate dried (Na_2SO_4), refiltered, and clarified with kieselguhr. The ether was distilled off, and the residue distilled at 0·4 mm. in an atmosphere of nitrogen. The crude distillate was redistilled at 15 mm. and had b. p. 142—144°. The *ester* contained phosphorus and chlorine (Found: F, 8·9. $C_4H_8O_3Cl_2FP$ requires F, 8·45%). (The slightly high fluorine content may be explained in that a modification of our usual technique was employed: it was necessary to use sufficient sodium to break the C–Cl as well as the P–F bonds, and this resulted in a final alcohol content of 15%, and a concentration of sodium chloride higher than is suitable in this analysis. These factors would cause coprecipitation of lead chloride with the chlorofluoride.)

Di-(2-fluoroethyl) Fluorophosphonate.—Phosphorus oxydichlorofluoride (24·0 g.) was placed in a Claisen flask fitted with a dropping-tube and calcium chloride outlet tube, and 2-fluoroethyl alcohol (22·5 g.) was added slowly, the temperature of the mixture (thermometer in the liquid) being kept at 0—5°. The hydrogen chloride evolved escaped through the calcium chloride tube. The mixture was set aside overnight and freed from hydrogen chloride by aeration as usual. The dark residue was distilled at 13 mm. and had b. p. 125—127°; yield, 15 g. (50%). The *ester* contained phosphorus (Found : F, 30·35. $C_4H_9O_2F_2P$ requires F, 29·6%).

Diphenyl Fluorophosphonate.—Dimethylaniline (60·5 g.) and phenol (47 g.) were mixed, and dry ether (50 c.c.) added. The mixture was cooled in ice-water, and phosphorus oxydichlorofluoride (34·3 g.) slowly run in. After standing overnight, the mixture crystallised spontaneously; more dry ether was added, and the dimethylaniline hydrochloride (*ca.* 70 g.) was filtered off. The ethereal filtrate was dried (Na_2SO_4), the ether distilled off, and the residue fractionated. The fraction of b. p. 115—118°/0·4 mm. was collected and redistilled at 106—108°/0·07 mm.; yield, 37·6 g. (60%) (Found : F, 7·93, 8·03. $C_{12}H_{10}O_3FP$ requires F, 7·54%).

Reaction between Ethylthiol and Phosphorus Oxydichlorofluoride.—(*a*) Ethylthiol was run into phosphorus oxydichlorofluoride, but no reaction occurred.

(*b*) Ethylthiol (10 g.) was dissolved in dry ether (50 c.c.) and sodium (3·7 g.) added. This mixture was added to a solution of phosphorus oxydichlorofluoride (12 g., 10% excess) in dry ether (50 c.c.). The ether was distilled off, and the residue fractionated. The fraction, b. p. 168—200°/20 mm., was refractionated and collected at 175°/18 mm.; a third distillation gave a fraction, b. p. 172—174°/16 mm. [Found : S, 40·46. $C_4H_{10}OFPS_2$ requires S, 34·04. $C_6H_{15}OPS_3$ requires S, 41·75%]. As the compound also contained phosphorus but no chlorine, it was considered to be *triethyl trithiophosphate*, and as it contained traces of fluorine it was probably contaminated with a small quantity of the ester described below.

(*c*) Dimethylaniline (60·5 g.) and ethylthiol (31 g.) were mixed, and phosphorus oxydichlorofluoride (34·25 g.) added in portions of *ca.* 5 g. The reaction was carried out at room temperature, and any rise in temperature checked by cooling in cold water. The mixture was kept for 2 days and then solidified on addition of a crystal of dimethylaniline hydrochloride. Dry ether was then added, and this hydrochloride (*ca.* 72 g.) filtered off. The filtrate was dried (Na_2SO_4), the ether distilled off, and the residue fractionated at 15 mm. The fraction of b. p. 104—107°/15 mm. was collected and found to be *diethyl fluorodithiophosphonate* (Found : F, 10·03, 9·7. $C_4H_{10}OFPS_2$ requires F, 10·1%). (Dimethylaniline has b. p. 90°/25 mm., and the trithio-ester, b. p. 174—175°/20 mm.).

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199. *A New Synthesis of* NN′*-Diarylformamidines.*

By W. B. WHALLEY.

A new synthesis of *NN′*-diarylformamidines is described. The method enables the facile detection of formic acid in admixture with other monobasic aliphatic acids.

THE chief methods described for the preparation of *NN′*-diarylformamidines are interaction of : (*a*) a primary aromatic amine with orthoformic ester (Claisen, *Annalen*, 1896, **287**, 366; v. Walther, *J. pr. Chem.*, 1886, **53**, 474); (*b*) an acid chloride with a mixture of a primary aromatic amine and the formanilide; (*c*) the complex 3HCl,2HCN (Gattermann, *Ber.*, 1883, **16**, 310) with primary aromatic amines (Dains, *Ber.*, 1902, **35**, 2496); (*d*) an arylamine with formic acid, heated under reflux with a catalyst such as boric acid plus iron filings (I.C.I., B.P. 353,138). The last is less well known.

The recent work of Lewis, Krupp, Tieckelmann, and Post (*J. Org. Chem.*, 1947, **12**, 303) throws considerable doubt upon the validity of procedure (*a*). These authors have shown that aniline and the three monochloroanilines react with orthoformic ester to produce compounds of the type $CH(NHR)_3$, and not amidines. Confusion between amidines and triarylaminomethanes has arisen owing to the close proximity of the melting points and nitrogen contents of the two series of compounds. The publication of Lewis *et al.* (*loc. cit.*) would thus appear to cast doubt upon the authenticity of other compounds prepared by method (*a*) and previously cited as formamidines. The values for the chlorine content of the compounds prepared by the present author indicate conclusively that they are amidine hydrochlorides and not mono- or di-hydrochlorides of the triarylaminomethanes.

The new method of preparation now to be described was discovered in the course of another investigation where it was necessary to detect small quantities of formic acid in admixture with other aliphatic monobasic acids, and is now published on account of its simplicity and the growing interest in *NN′*-diarylformamidines as synthetical intermediates (cf. Grothaus and Dains, *J. Amer. Chem. Soc.*, 1936, **58**, 1334; Meyer and Wagner, *J. Org. Chem.*, 1943, **8**, 239). The process can be used for the detection of formic acid as above because all other monobasic

aliphatic acids, as well as dibasic aliphatic acids and the aromatic acids, react to form only the corresponding *N*-substituted amide.

According to the present method, *NN′*-diarylformamidines are prepared by refluxing an anhydrous mixture of a primary aromatic amine, its hydrochloride, and sodium formate. Reaction is complete in 10—15 minutes. The method, which has been applied to the preparation of several formamidine hydrochlorides, fails with benzidine and strongly negatively substituted bases such as the nitroanilines (cf. Dains, *loc. cit.*). Where other conditions are normally favourable, reaction proceeds slowly, if at all, in the absence of hydrogen chloride (cf. Hübner *et al.*, *Ber.*, 1877, **10**, 1720, 2165; Friedmann and Backeberg, *J.*, 1938, 469).

Experimental.

General Method for Preparation of NN′*-Diarylformamidines.*—Finely powdered anhydrous sodium formate is mixed with an equal weight of amine hydrochloride and five times the weight of amine. The mixture is heated under reflux for 15 minutes, although reaction is probably completed in 5 minutes. The cooled reaction mixture is acidified with 2N-hydrochloric acid (15 vols.), and the *NN′*-diarylformamidine hydrochloride separates as a crystalline mass. The product may be collected and recrystallised, in many cases from dilute hydrochloric acid, although this is not always possible, or it may be converted into the free base by any of the usual methods.

It will be noted that the efficacy of the method is largely dependent upon two requirements: (*a*) that the hydrochloride of the amidine should be much less soluble in dilute hydrochloric acid than the hydrochloride of the amine itself, and (*b*) that the m. p. of the amine should be low enough to allow it to function as the solvent for the reaction. Both these requirements are met by the majority of the common aromatic primary amines.

The yield of formamidine hydrochloride is at least 40% (as with aniline and *m*-xylidine), but often as high as 80—90% (as with *p*-toluidine); in general, the yields are nearer the higher limit than the lower one.

All m. p.s were determined in sealed tubes, but they are of doubtful value. They appear to be reproducible with difficulty, owing to dependence upon the rate of heating and the sublimation of several of the products.

NN′-Diphenylformamidine hydrochloride was obtained in colourless needles, m. p. 251° (decomp.), from dilute aqueous hydrochloric acid, or in platelets, m. p. 251° (decomp.), from ethyl acetate containing a trace of hydrogen chloride [Found: N, 12·1; Cl, 15·2. Calc. for $C_{13}H_{13}N_2$,HCl: N, 12·1; Cl, 15·3%. Calc. for $CH(NHPh)_2$,HCl: N, 12·9; Cl, 10·8%. Calc. for $CH(NHPh)_2$,2HCl: N, 11·3; Cl, 19·3%). Nef (*Annalen*, 1892, **270**, 297) records m. p. 255° for $C_{13}H_{12}N_2$,HCl,3H_2O, and Friedmann and Backeberg (*loc. cit.*), using method (*b*), record m. p. 259°.

NN′*-Di-*(o*-tolyl)formamidine hydrochloride* was obtained in colourless needles, m. p. 205° (decomp.), after crystallisation from dilute aqueous hydrochloric acid (Found: N, 10·2; Cl, 13·5. $C_{15}H_{16}N_2$,HCl requires N, 10·8; Cl, 13·5%). The *m*-tolyl salt crystallised in colourless needles, m. p. 214° (decomp.), from dilute aqueous hydrochloric acid (Found: N, 10·5; Cl, 13·80%). Von Niementowski (*Ber.*, 1887, **20**, 1893) records m. p. 214° (decomp.) for a specimen prepared by prolonged boiling of the formyl derivative of *m*-toluidine.

NN′*-Di-*(p*-tolyl)formamidine hydrochloride* crystallises in colourless needles, m. p. 228—230° (decomp.), from a large volume of very dilute aqueous hydrochloric acid (Found: N, 10·1; Cl, 12·5%). Senier (*Ber.*, 1885, **18**, 2296) records the preparation of this compound but no m. p. or analysis.

NN′-Di-(*m*-xylyl)formamidine hydrochloride crystallises in colourless needles, m. p. 236° with decomposition and sublimation, from dilute aqueous hydrochloric acid (Found: N, 9·4; Cl, 11·9. Calc. for $C_{17}H_{20}N_2$,HCl: N, 9·7; Cl, 12·3%). Dains (*loc. cit.*), using method (*c*), records m. p. 243° (decomp.).

NN′*-Di-*(o*-chlorophenyl)formamidine hydrochloride* crystallises in large, colourless, square-ended prisms, subliming at about 250°, from dilute aqueous hydrochloric acid (Found: N, 9·0; Cl, 36·4. $C_{13}H_{10}N_2Cl_2$,HCl requires N, 9·3; Cl, 35·5%). The m*-chlorophenyl* salt was obtained in buff-coloured needles, m. p. 298° (decomp.), insoluble in very dilute hydrochloric acid and purified by extraction with hot dilute hydrochloric acid (Found: N, 9·1; Cl, 34·0%).

NN′-Di-(*ψ*-cumyl)formamidine hydrochloride crystallised in colourless needles, m. p. 236° (decomp.), from aqueous hydrochloric acid. Dains (*loc. cit.*), using method (*c*), records m. p. 236° (decomp.) (Found: N, 9·1; Cl, 10·9. Calc. for $C_{19}H_{24}N_2$,HCl: N, 8·9; Cl, 11·2%).

Detection of Formic Acid in Admixture with Other Aliphatic Monobasic Acids.—Prepared from the acids, the well-powdered sodium salts (1 part) are mixed with aniline hydrochloride (5 parts) and freshly distilled aniline (10 parts) and heated under refluxed for 15 minutes. After cooling, the darkened solution is acidified with 2N-hydrochloric acid (100 parts). *NN′*-Diphenylformamidine hydrochloride crystallises out immediately or on cooling, and after standing for 5 minutes is removed by filtration, and washed with a very small quantity of 2N-hydrochloric acid. The product may be further purified by recrystallisation from dilute aqueous hydrochloric acid.

The anilides of higher aliphatic acids may separate out from the filtrate on standing, but more usually have to be removed by ether extraction, followed by purification in the normal way.

University of Liverpool. [*Received, July* 16th, 1947.]

200. *The Thermochemistry of Solutions. Part V. The Heats of Ionisation of Some Organic Acids.*

By T. L. Cottrell, G. W. Drake, D. L. Levi, K. J. Tully, and J. H. Wolfenden.

Using the calorimeter described in Part I (*J.*, 1934, 1362), the heats of ionisation of several organic acids have been measured in dilute solution over the temperature range 10—30°. The results have been combined with dissociation-constant data to give the thermodynamic functions for ionisation. The acids examined were: butyric, *iso*butyric, hexoic, *iso*valeric, β-chloropropionic, benzoic, *m*- and *p*-hydroxybenzoic, *m*- and *p*-nitrophenol, and *o*-chlorophenol. Less accurate data for *n*-valeric and trimethylacetic acids are also provided.

The object of the present paper is to present concisely the results of a series of thermochemical measurements made in 1938—1941 on the ionisation of some organic acids. The thermodynamics of acid–base equilibria continue to be the subject of active interest and controversy, and it is hoped that the data here set out will add to the reliable information available to test any theoretical treatments. The calorimetric measurement of heats of ionisation gives values which, for the concentration used, are comparable in accuracy with those derived from the temperature variation of dissociation constants as measured by the precise E.M.F. method of Harned and his collaborators (cf. Harned and Owen, " The Physical Chemistry of Electrolytic Solutions ", New York, 1943). The main uncertainty in the results is not the experimentally measured quantity, but its correction to infinite dilution, because of the well-known specificity of the heats of dilution of electrolytes. However, the heats have been measured at concentrations (M/20 or less) at which the heat of dilution corrections are fairly small, and where the limiting law furnishes at least a rough guide to their values.

The measurements were carried out at 10°, 20°, and 30° for all the acids except β-chloropropionic acid, which was only examined at 20° and 30°. The resulting heats of ionisation give the change in heat content of the reaction directly, and, when combined with free-energy data at one temperature, the value of the entropy change.

Experimental.

Calorimeter.—The calorimeter for heats of dilution and the general procedure described in Part I (*loc. cit.*) were used with a few minor modifications. For the measurements with butyric, *iso*butyric, *iso*valeric, hexoic, β-chloropropionic, benzoic, *p*-hydroxybenzoic, and most of those with *m*-hydroxybenzoic, the multiple-junction thermel described in Part IV (*J.*, 1939, 118) was used; for the remaining acids a thermel of slightly lower sensitivity but much lower thermal inertia constructed by D. McEwan was used.

In McEwan's thermel the ebonite formers employed in the previous design were eliminated. The rows of copper–constantan junctions were held in position by a framework of thin steel rods soldered at each end to a semicircular brass plate, and insulated from the thermel by lengths of insulation sleeving.

The heat capacity of the calorimeter was determined by carrying out the neutralisation of hydrochloric acid with sodium hydroxide, for which accurate values of ΔH have been given by Richards and Rowe (*J. Amer. Chem. Soc.*, 1922, **44**, 684).

Reaction Measured.—The reaction of which the heat content change was measured was

$$NaA + HCl = NaCl + HA \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It was assumed that the sodium salt of the acid was completely dissociated; the heat change therefore corresponded to that of the reaction

$$A^- + H^+ = HA \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

plus that due to the dilution of the reactant in excess. A 10% excess of hydrochloric acid was used in order to suppress ionisation of the acid formed, and the solutions of the sodium salts contained between 2 and 3% of the free acid to ensure that there was no free alkali present. The values of ΔH_e recorded are those of the reverse of reaction (2), per mole. of acid, but they include the small contribution due to the heats of dilution.

Procedure.—25 Ml. of a solution of the sodium salt of the acid, generally 0·05M, were pipetted into the inner compartment of the calorimeter, 25 ml. of the hydrochloric acid solution into the outer compartment, and the temperature change on mixing determined as previously described. In some cases the concentrations had to be reduced because of the insolubility of the acid.

Materials.—The acids were pure commercial samples, further purified by distillation or crystallisation. Standard methods were used for the preparation of the sodium hydroxide and hydrochloric acid solutions.

Results.—To obtain ΔH from the observed temperature change, a knowledge of the specific heat of the resultant solutions is required. In many cases this was not available, but in view of the fact that they were all very dilute a value of 0·995 was adopted throughout. Only a small error is liable to be introduced by this approximation.

The results are given in Table I.*

TABLE I.

Acid.	Concn. of soltns. Salt.	HCl.	ΔH_c (cals.).† 10°.	20°.	30°.	$\Delta H°$ (cals.). 10°.	20°.	30°.
Butyric	0·050	0·0555	−114± 5 (±4)	−392± 7 (±3)	−677±10 (±3)	−242	− 542	− 853
*iso*Butyric	0·050	0·0555	−217± 6 (±4)	−473± 9 (±4)	− 745±11 (±4)	−345	− 623	− 921
Hexoic	0·050	0·0555	−69± 5 (±4)	−343± 6 (±3)	− 617±10 (±4)	−197	− 493	− 793
*iso*Valeric	0·050	0·0555	−639±10 (±4)	−889±13 (±4)	−1126±15 (±4)	−767	−1039	−1302
β-Chloropropionic	0·050	0·0555	—	−307± 7 (±4)	− 553±10 (±4)	—	− 457	− 729
p-Hydroxybenzoic	0·0194	0·0215	1025±33 (±23)	—	—	—	—	—
p-Hydroxybenzoic	0·0320	0·0352	—	681±27 (±20)	307±23 (±20)	945	561	167
Benzoic	0·0151	0·0172	694±28 (±21)	—	—	—	—	—
Benzoic	0·0191	0·0215	—	389±20 (±16)	41±19 (±18)	622	295	−68
m-Hydroxybenzoic	0·0501	0·0566	785±18 (±10)	501±17 (±12)	149±11 (±10)	655	348	−29
m-Nitrophenol ...	0·0513	0·0566	5273±69 (±16)	4984±63 (±13)	4751±62 (±14)	5145	4833	4575
p-Nitrophenol ...	0·0515	0·0566	5023±66 (±16)	4820±61 (±13)	4642±59 (±13)	4895	4669	4466
o-Chlorophenol ...	0·0515	0·0566	5229±68 (±16)	4946±65 (±16)	4563±60 (±14)	5101	4795	4387

† The total probable error is given immediately after the ΔH value. The figure in parentheses is the probable error due to random error from determination to determination.

The estimates of the error in ΔH_c were arrived at in the following way. The random error was obtained by means of an analysis of the results, grouping comparable experiments together, and applying Peters's formulæ to obtain the probable errors. Each ΔH value quoted is the mean of at least three determinations, the variation in the probable error from value to value being due to the fact that all the results are not the mean of the same number of observations. The probable error given in parentheses in Table I is the error obtained in this way. It was considered that systematic errors might be due to (*a*) error in the heat capacity of the calorimeter, (*b*) error in the specific heat of the solutions, (*c*) error due to inaccuracies in making up solutions. The effect of these errors is proportional to the temperature change, and a total of 1% of the observed ΔH values was allowed for them. The total uncertainty, taking both systematic and random errors into account, is given immediately after the ΔH values in the table. The values of $\Delta H°$, the heat content change at infinite dilution, recorded are those obtained by applying the Debye–Huckel limiting law uniformly to all the electroytes present, and neglecting the heat of dilution of the undissociated acid; ΔH_D, the heat absorbed when an infinite quantity of solvent is added to a solution is given, for a uni-univalent electrolyte, by the expression

$$\Delta H_D = Ne^2\sqrt{\frac{8\pi Ne^2}{1{,}000\epsilon kT}}\cdot\frac{1}{\epsilon}\left(1+\frac{T}{\epsilon}\frac{\partial\epsilon}{\partial T}+\frac{1}{3}\frac{T}{V}\frac{\partial V}{\partial T}\right)\sqrt{c}$$

(cf. Fowler and Guggenheim, "Statistical Thermodynamics", Cambridge, 1939, p. 404). Neglecting the term for the expansion of the solution, and inserting numerical values, we have $\Delta H = -398\sqrt{c}$, $-469\sqrt{c}$, and $-547\sqrt{c}$ cals. for temperatures of 10°, 20°, and 30°, respectively. These figures differ slightly from those given elsewhere (cf. Harned and Owen, *op. cit.*) because of the use of Wyman and Ingalls's data for the dielectric constant of water (*J. Amer. Chem. Soc.*, 1938, **60**, 1182) and the values of N, e, and k recommended by Birge (*Rep. Prog. Physics*, 1941, **8**, 90; see also *J.*, 1946, 219).

DISCUSSION.

The usefulness of the $\Delta H°$ values given in Table I for a discussion of the thermodynamic functions for ionisation of the acids is chiefly limited by the uncertainty of the Debye–Huckel correction. The deviations from the limiting law are, however, always of the same sign, and it is therefore reasonable to consider that the corrections applied represent a maximum, and that where the true value of $\Delta H°$ differs from that given, it lies nearer to the observed value of ΔH_c

* Similar measurements carried out with *n*-valeric and trimethylacetic acids at 10°, 20°, and 30° were less reliable because of persistent temperature drifts. The plots of ΔH_c against T were not linear, ΔC_p appearing to decrease numerically with temperature. Although the data are not of comparable precision with that of those in the table, we think it worth recording that they lead to the following values of ΔH_c at 25°: *n*-valeric acid, − 520 ± 50 cals.; trimethylacetic acid, − 640 ± 100 cals.

at the concentration used. In his work on the heats of ionisation of some acids and bases at comparable concentrations, Pitzer (*J. Amer. Chem. Soc.*, 1937, **59**, 2365) also corrected his observed values to infinite dilution by means of the Debye–Huckel theory, and gives an estimate of the uncertainty of his final results, but does not given any clear indication of how it was derived. It does not appear possible to give a satisfactory estimate of the uncertainty of $\Delta H°$, but it can be said that our values of the probable error of the observed quantity give a lower limit to the heat of ionisation, and that a comparison of the results with those obtained by making an estimate of the heats of dilution by analogy with experimental data for similar substances suggests that they are not in error by more than about 60 cals. Detailed consideration of the results for butyric acid suggests that our $\Delta H°$ values are rather more reliable at higher temperatures.

Values of ΔC_p have been obtained from the variation of $\Delta H°$ with temperature and these values, together with $\Delta S°_{298·1}$ values obtained by combination of the results with dissociation-constant data, are given in Table II. The values of $\Delta H_{298·1}$ were obtained by interpolation; $\Delta C_{p298·1}$ is recorded. For those acids for which ΔC_p varies with temperature, ΔC_p at other temperatures may be obtained from the data in Table I. These values are discussed below.

TABLE II.

The thermodynamic functions for ionisation of some acids at 25° (in cals.).

Acid.	$\Delta C_p°_{298·1}$.	$\Delta H°_{298·1}$.	$\Delta S°_{298·1}$.	$\Delta G°_{298·1}$.	Lit. ref. for $\Delta G°$.
Butyric	−30·6	− 698	−24·4	6,574	(1)
*iso*Butyric	−28·8	− 775	−24·8	6,622	(2)
Hexoic	−29·8	− 644	−24·5	6,648	(2)
*iso*Valeric	−27·0	−1168	−25·7	6,509	(2)
β-Chloropropionic	−27·2	− 593	−20·2	5,435	(3)
Benzoic	−35	110	−18·9	5,750	(4)
p-Hydroxybenzoic	−39	363	−19·8	6,270	(6)
m-Hydroxybenzoic	−38 *	159	−18·1	5,561	(5)
m-Nitrophenol	−26	4705	−22·1	11,280	(8)
p-Nitrophenol	−22	4570	−17·4	9,755	(9)
o-Chlorophenol	−41 *	4590	−23·5	11,580	(7)

* From 20° to 30°; the value from 10° to 20° is significantly different, and may be calculated from the $\Delta H°$ values in Table I.

References. (1) Harned and Sutherland (quoted by Harned and Owen, *op. cit.*). (2) Dippy (*J.*, 1938, 1222). (3) Dawson and Key (*Proc. Leeds Phil. Soc., Sci. Sectn.*, 1934, **2**, 296). (4) Rule and La Mer (*J. Amer. Chem. Soc.*, 1938, **60**, 1981). (5) Euler, quoted by Everett and Wynne-Jones (*Trans. Faraday Soc.*, 1939, **35**, 1380). (6) Jones and Speakman (*J.*, 1944, 19), calculated to 25° using our value of ΔH. (7) Murray and Gordon (*J. Amer. Chem. Soc.*, 1935, **57**, 110); this value is probably rather unreliable because the result was obtained in 50% methanol solution, and corrected to pure water on the assumption that the effect of methanol would be the same as its effect on the dissociation constant of phenol. (8) Lundén (*J. Chim. physique*, 1907, **5**, 574). (9) *Idem* (*Z. physikal. Chem.*, 1910, **70**, 249).

Aliphatic Acids.—Comparison with E.M.F. data is possible only for butyric acid, for which the thermodynamic dissociation constant K, has been measured from 0° to 60° by Harned and Sutherland (cf. Harned and Owen, *op. cit.*, Chap. 15). Their data give $\Delta H_{298·1}$ as − 693 cals., in excellent agreement with our value of − 698 cals. For ΔC_p, however, their results yield − 36·4 cals. per degree, compared with our value of − 30·6. Using our values of $\Delta H°_{20°}$ and ΔC_p, Harned's value for $K_{20°}$, and the empirical equation (15 − 6 − 9) of Harned and Owen (*op. cit.*), we obtain values for K at 10° and 30° which agree with Harned's within his experimental error, as shown below, although use of our ΔC_p value outside this temperature

	10°	20°	30°
10^5K, calc.	1·579	1·542	1·482
10^5K, obs.	1·576	1·542	1·484

range does not give agreement with Harned's dissociation constants. This suggests that our value of ΔC_p may be slightly too small, which could be accounted for if the deviations from the theoretical heat of dilution correction were greater at lower temperatures. In view of this, it seems reasonable to suggest that our numerical values of ΔC_p represent a lower limit.

Little comment on the values for the other unsubstituted aliphatic acids is necessary, except to point out that they confirm the general picture of the ionisation of fatty acids as discussed by Everett and Wynne-Jones (*loc. cit.*). It is noteworthy that for *iso*valeric acid, if we assume that the heat of dilution correction is zero at 10° and the full amount predicted by the limiting

law at 30°, ΔC_p cannot be greater than − 33, confirming that the fall in ΔC_p with increasing chain length, observed from formic to butyric acid, is real. β-Chloropropionic acid shows a markedly smaller entropy loss on ionisation, presumably because of its greater polarity (cf. Magee, Ri, and Eyring, *J. Chem. Physics*, 1941, **9**, 419).

Aromatic Acids.—For benzoic acid, Everett and Wynne-Jones (*loc. cit.*) have deduced from Schaller's data the values of 40 and − 36·2 for $\Delta H°_{298\cdot1}$ and ΔC_p, respectively. The ionisation constant of benzoic acid has been measured at 5°, 25°, and 45° by Rule and La Mer (*J. Amer. Chem. Soc.*, 1938, **60**, 1981) and by applying Harned and Embree's empirical equation,

$$\log K - \log K_\theta = - p(t - \theta)^2,$$

with $p = 5 \times 10^{-5}$ which implies a value of − 40 cals. per degree for ΔC_p (cf. Harned and Owen, *loc. cit.*), we obtained $\Delta H°_{298\cdot1} = 191$ cals.* Our values of 110 cals. and 35 cals./degree are in good agreement with these results. For *m*-hydroxybenzoic acid, Everett and Wynne-Jones using Schaller's data give $\Delta H°_{298\cdot1}$ as 170 cals. and $\Delta C_p = - 29\cdot9$. Our value of 159 cals. for $\Delta H°_{298\cdot1}$ is in excellent agreement, but we find that ΔC_p varies with temperature, being − 31 from 10° to 20°, and − 38 from 20° to 30°. The value quoted by Everett and Wynne-Jones is therefore almost certainly low.

Phenols.—Our result do not agree with the ΔH and ΔC_p values derivable from dissociation constants due to Lundén (*locc. cit.*) for *m*- and *p*-nitrophenol. His dissociation constants are from conductivity measurements, and they vary so widely with dilution that agreement with the present series is hardly to be expected. Our data are not sufficiently comprehensive to allow of a discussion on the influence of substituents on the thermodynamics of the ionisation of phenols.

We wish to express our thanks to the Royal Society for a grant which defrayed the cost of some of the apparatus used, and to the Chemical Society for a grant for the purchase of chemicals.

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201. *The Thermochemistry of Solutions. Part VI. The Heat of Ionisation of Succinic Acid.*

By T. L. COTTRELL and J. H. WOLFENDEN.

Using a technique similar to that described in Part V (preceding paper), we have measured calorimetrically the heats of the first and the second ionisation of succinic acid at two concentrations over the temperature range 5—30°. The results have been used to obtain the heat-content change and the heat-capacity change at infinite dilution, and have been combined with ionisation-constant data to give the thermodynamic functions for the two stages of ionisation. The thermodynamics of the ionisation of dibasic acids is discussed in the light of the results, with special reference to the Kirkwood–Westheimer theory.

SINCE the publication of Kirkwood and Westheimer's theory of the electrostatic effect of substituents on the dissociation constants of organic acids (*J. Chem. Physics*, 1938, **6**, 506, 513), considerable interest has been taken in the dissociation constants of dibasic acids (cf. Westheimer and Shookhoff, *J. Amer. Chem. Soc.*, 1939, **61**, 555; Wynne-Jones and Rushbrooke, *Trans. Faraday Soc.*, 1944, **40**, 99; Westheimer and Kirkwood, *Trans. Faraday Soc.*, 1947, **43**, 77). It is agreed that the theory is inadequate to explain the temperature dependence of the effect, but there are no very reliable measurements of the variation of both ionisation constants of dibasic acids with temperature against which the theory can be checked. The present work is an attempt to contribute relevant data towards such a discussion.

In Part V the difficulty of obtaining ΔH values at infinite dilution from calorimetric results was discussed, and it was shown that use of the Debye–Huckel limiting law gave results which were comparable with those obtained by other means. Although the limiting law therefore has been shown to give a reasonably good approximation to the behaviour of uni-univalent electrolytes, the validity of the correction for uni-bivalent electrolytes is much less certain; ΔH was therefore measured both in 0·05M- and in 0·025M-solutions, in order to obtain some indication of how ΔH varies with concentration.

As some of the results in Part V suggested the possibility that ΔC_p was not independent of

* Although Harned and Embree's equation is only an approximation, it was applied in preference to the other empirical equations for the variation of log K with T because it is easier to fit to the data, and because in any case Rule and La Mer's results are not sufficiently precise to warrant fitting to a more exact expression.

temperature, the temperature range was extended downward to 5°. It would have been useful to extend the measurements to higher temperatures also, but control of the temperature of the bath surrounding the calorimeter was not sufficiently good above 30° to make this worth while.

Experimental.

Calorimeter.—The calorimeter was of similar design to that used previously, but was larger, its capacity being 100 instead of 50 ml. A new thermel was constructed; it consisted of 112 junctions of chromel–constantan. The junctions were spot-welded instead of soldered as previously, the chromel being introduced because a chromel–constantan junction has a greater thermal E.M.F. than a copper–constantan one (cf. Weber, " Temperature Measurement and Control ", Philadelphia, 1941, Chap. IV), and because chromel gives a better spot-weld.

The sensitivity of the thermel was very much greater than that of those previously used, partly on account of the increased thermal sensitivity of the new junctions, and partly because mechanical improvements resulting in more accurate rotation of the calorimeter enabled the junctions to be mounted closer to it. The resistance of the thermel and leads was 15·5 ohms, and by using a Tinsley galvanometer of sensitivity 790 mm. per micro-amp., and internal resistance 134 ohms, a sensitivity of 10,000 mm. per ° c. was obtained. This is to be compared with 3,000 mm. for the thermel described in Part IV, and about 1,000 for that constructed by McEwan and used for some of the other work on acids.

The chief advantage of a sensitive thermel is not that increased accuracy is obtained, because thermel sensitivity does not appear to be the limiting factor, but that operation of the adiabatic control is made easier and the effect of any parasitic e.m.f.'s which might arise in the thermel circuit, and which tend to cause temperature drifts, is minimised.

The heat capacity of the calorimeter was determined by carrying out the dilution of $KNO_3,50H_2O$ to $KNO_3,100H_2O$, for which accurate values of ΔH and its temperature coefficient have been given by Richards and Rowe (*J. Amer. Chem. Soc.*, 1921, **43**, 770).

Reaction measured.—Essentially the same reaction was carried out as described in Part V, but modifications in the concentrations of the reactants were necessary. For the first ionisation, the reaction was

$$NaHA + HCl \longrightarrow NaCl + H_2A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

To ensure that none of the doubly-charged anion was present in the sodium hydrogen succinate solution, a large excess of free succinic acid was present. The solution was 0·05M in sodium hydrogen succinate, and approximately 0·25M in free succinic acid. A 10% excess of hydrochloric acid solution was used. Half these concentrations were used in the measurements at higher dilution. For the second ionisation, the reaction was

$$Na_2A + 2HCl \longrightarrow 2NaCl + H_2A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The solutions were 0·05M and 0·025M in sodium succinate, and the same excess of hydrochloric acid was used as before. Thus the reactions for which ΔH is recorded are :—

$$H_2A = H^+ + HA^- \quad (\Delta H_1)$$
$$\text{and} \quad H_2A = 2H^+ + A^= \quad (\Delta H_1 + \Delta H_2)$$

and contributions due to the heats of dilution of the reactants are included. These may not be small, and are discussed below.

Materials.—" AnalaR " Succinic acid was used, and standard methods were used for the preparation of sodium hydroxide and hydrochloric acid solutions. The solutions of the acid salt were found to be readily affected by fungoid contamination. They were therefore used immediately after being prepared.

Results.—The specific heat of the solution from reaction (1) was taken to be 0·990, and that from reaction (2) 0·995. The experimental results are set out in the table.

Observed ΔH *values.*

(ΔH_1).				$(\Delta H_1 + \Delta H_2)$.			
0·05M.		0·025M.		0·05M.		0·025M.	
Temp.	ΔH (cals.).	Temp.	ΔH.	Temp.	ΔH.	Temp.	ΔH.
5·30°	1245	10·44°	1085	5·51°	2608	4·65°	2532
5·54	1245	13·50	1085	5·84	2573	4·89	2555
13·37	978	17·64	882	9·93	2221	9·80	2175
16·58	913	19·33	860	10·14	2188	9·95	2185
20·44	794	25·61	613	10·20	2153	17·39	1615
26·25	558	27·11	656	18·07	1529	17·86	1627
29·69	547	29·49	558	18·10	1512	29·13	594
30·14	496	—	—	18·20	1529	30·58	560
30·34	468	—	—	29·93	702	—	—
33·64	408	—	—	30·00	722	—	—

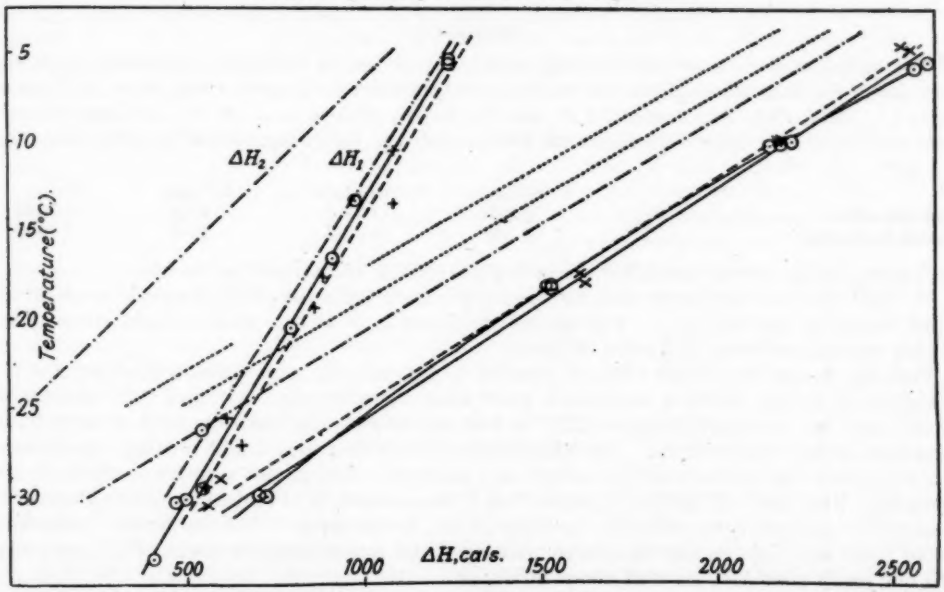
For the first stage of ionisation in 0·05M-solutions, the plot of ΔH against temperature was linear, and the results were fitted to a straight line by the method of least squares, giving the result $\Delta H = 1399 - 29{\cdot}99t$ cals., where t is the temperature in °c. The probable error of a single determination was ± 18 cals., which is comparable with the precision attained in the earlier work using the McEwan thermel, but slightly less than that attained with the aliphatic acids. Estimation of the probable error in the expression for ΔH gives $\Delta H = (1399 \pm 5{\cdot}6) - (29{\cdot}99 \pm 0{\cdot}24)t$ cals. The plot of ΔH against T was also linear for 0·025M-solutions, and the results were fitted to a straight line by the method of least

squares, giving $\Delta H = (1429 \pm 13) - (29{\cdot}78 \pm 0{\cdot}61)t$ cals. The probable error of a single determination was $\pm$ 35 cals., almost exactly double that for 0·05M-solutions. This is, of course, in agreement with expectation.

For the first and the second stage of ionisation together, the results for 0·05M-solutions were fitted to a straight line by the method of least squares, giving $\Delta H = 2975 \pm 77{\cdot}03t$ cals. When fitted to a straight line, the probable error of a single determination comes out at $\pm$ 39 cals., which is much greater than that found for ΔH_1 in 0·05M-solutions. The results were better fitted by a parabolic expression, which gives $\Delta H = 1722{\cdot}5 - 80{\cdot}60\ (t - 15{\cdot}592) + 0{\cdot}708\ (t - 15{\cdot}592)^2$ cals., and the probable error of a single determination $\pm$ 12 cals. The overall accuracy of the results is not, however, in our opinion sufficient to place this deviation from linearity beyond doubt. The results for 0·025M-solutions were fitted to a straight line, giving $\Delta H = (2948 \pm 11) - (78{\cdot}37 \pm 0{\cdot}64)t$ cals., and $\pm$ 33 cals. for the probable error of a single determination; this is in agreement with the expected probable error.

It should be noted that the probable errors quoted above refer only to the random errors. As in Part V, allowance must be made for systematic errors, such as those in the heat capacities of calorimeter and solutions, and possible inaccuracies in preparation of solutions. This may contribute an uncertainty of not more than 1% to the observed ΔH.

Variation of heat of ionisation with temperature.



——O— ΔH_1, $(\Delta H_1 + \Delta H_2)$ *at* 0·05M; – – + – – ΔH_1 *at* 0·025M; – – × – – $(\Delta H_1 + \Delta H_2)$ *at* 0·025M; — . — . — *values adopted for* $\Delta H_1°$, $\Delta H_2°$, *and* $(\Delta H_1° + \Delta H_2°)$. *The two dotted lines represent the values of* $(\Delta H_1 + \Delta H_2)$ *obtained by direct application of the limiting law for heats of dilution to the experimental results at* 0·05M (*upper line*) *and* 0·025M (*lower line*).

Dilution Corrections.—In obtaining $\Delta H_1°$, the heat content for the first ionisation at infinite dilution, there are two uncertainties to be taken into account: (1) The uncertainty in the heat of dilution of excess succinic acid, which is too great to be neglected, but too small to be measured accurately by our methods. (2) The usual uncertainty in the application of the limiting law to the heat of dilution of electrolytes.

(1) As a guide to the magnitude of this correction, the heat of dilution of 0·25M-succinic acid to 0·125M was measured at 20°. The result was $\Delta H = +$ 13 cals. per mole, the uncertainty in this value being about $\pm$ 3 cals. This means that the correction to ΔH per mole of sodium salt for 0·05M-solutions is about + 65 cals. If it is assumed that the heat of dilution varies linearly with concentration, the molar heat of dilution of 0·125M-succinic acid to half that concentration will be 6·5 cals., and the correction to ΔH in 0·025M-solutions about + 33 cals. In view of the fairly large uncertainty of this correction, it was taken to be temperature independent. With this correction applied, ΔH_1 in 0·05M- and 0·025M-solutions is given respectively by $\Delta H_1 = 1464 - 30{\cdot}0t$ cals., and $\Delta H_1 = 1462 - 29{\cdot}8t$ cals.

(2) The limiting law predicts a fall of about 45 cals. in ΔH from 0·05M to 0·025M, while the experimental results show no significant alteration, although in view of the probable errors a drop of some 20—30 cals. is not ruled out. The deviation from the limiting law is in the expected direction. However, the limiting law might be expected to apply more nearly to the dilution to infinity of 0·025M-solutions than that of 0·05M-solutions, and the correction has therefore been applied to the results at the former concentration. Although the predicted limiting-law correction does not vary linearly with temperature, the nature of the approximations made is such that the small predicted deviation from linearity of the $\Delta H_1°$ plot against temperature is not significant. Adopting this procedure between 5° and 30°, we may represent our results for $\Delta H_1°$ by the equation $\Delta H_1° = 1390 - 31{\cdot}5t$ cals.

To obtain ΔH°_2 we have to subtract ΔH_1° from the measured value of ΔH for reaction (2), corrected to infinite dilution. The correction of ΔH for reaction (2) is difficult because of the inapplicability of the limiting law for multivalent electrolytes except at very low concentrations. The situation is further complicated by the fact that, although at 5° and 30° the drop in ΔH from 0·05M to 0·025M is not much less than that required by the theory, yet the curvature of the plot of ΔH against T for the 0·05M-solution means that in the region 15—20° the drop is very small compared with the theoretical value of about 150 cals. (For a uni-bivalent electrolyte, the limiting slope for heat of dilution is $3\sqrt{3}$ times that for a uni-univalent electrolyte.) There is no obvious explanation for this discrepancy.

Accordingly, we have adopted a rather arbitrary procedure for obtaining ΔH°. We have taken values for ΔH at 0·05M and 0·025M as obtained from the linear equations, and obtained a value at 0·01M by extrapolation, assuming a linear dependence of ΔH on concentration. We have then applied the limiting law to these values. The result of this procedure may be expressed as $(\Delta H_1^\circ + \Delta H_2^\circ) = 2737 - 83{\cdot}7t$ cals. On this basis $\Delta H_2^\circ = 1347 - 52{\cdot}2t$ cals.

It is obvious that the results at infinite dilution, particularly for the second stage of ionisation, are subject to considerable uncertainty. The figure shows the experimentally determined heats of ionisation, and the heats of ionisation at infinite dilution derived from them by the method described above, and gives some idea of the nature of the approximations involved. For the first and the second stage of ionisation together, the effect of applying the limiting law directly is shown.

Discussion.

The only e.m.f. data on succinic acid which appear to be sufficiently accurate to warrant their use in the derivation of the thermodynamic functions for ionisation are those of Jones and Soper (*J.*, 1936, 133), who measured K_1 and K_2 for ten dibasic acids at 25°, 50°, and 74°. We have combined our data with theirs at 25° to give the following values for ΔH°, ΔC_p°, ΔS°, and ΔG° :

	$\Delta H^\circ_{298\cdot1^\circ}$	$\Delta C_p^\circ{}_{298\cdot1^\circ}$	$\Delta S^\circ_{298\cdot1^\circ}$	$\Delta G^\circ_{298\cdot1^\circ}$
First ionisation	+602	−31·5	−17·0	+5680
Second ionisation	+ 42	−52·2	−25·5	+7650

The results for the second ionisation are rather less reliable than those for the first.

By using Jones and Soper's data for the temperature variation of K, it should be possible to obtain values of ΔH and ΔC_p. The accuracy claimed in K is 1%, which should allow at least roughly reliable values of ΔC_p to be obtained.

Plotting Jones and Soper's log K against T for succinic acid showed that for the first ionisation K cannot reach a maximum until somewhere between 50° and 74°, whereas our results show on extrapolation that $\Delta H_1^\circ = 0$ at about 45°, and therefore that K must have a maximum at this temperature. The disagreement is marked, but might possibly be explained by a decrease in the numerical value of our ΔC_p above 30°, though this is rather unlikely, in view of the fact that none of Harned's precise e.m.f. measurements of ionisation constants over the range 0—60° shows any appreciable variation of ΔC_p in this range. For the second ionisation, a plot of Jones and Soper's results showed that log K has a maximum at about 25°, in agreement with our result that $\Delta H_2^\circ = 0$ at about 26°.

The disagreement with our results for ΔH_1° made us interested in the results which might be obtained by applying three-constant expressions to the ionisation constants of all the acids investigated by Jones and Soper. We used expressions of the forms used by Harned and Robinson (*Trans. Faraday Soc.*, 1940, **36**, 973) and by Everett and Wynne-Jones (*ibid.*, 1939, **35**, 1380) to calculate ΔC_p. The two equations gave results in close agreement. Since only three points are available it is not possible to say how well the true variation of K with T is represented, and therefore any conclusions based on such a treatment must be tentative. Below we give values of ΔC_p, rounded to the nearest 5 cals., for the acids investigated by Jones and Soper.

Acid.	ΔC_p. 1st Ionisation.	2nd Ionisation.
cis-Caronic	−50	−25
*cyclo*Hexane-1 : 1-diacetic	−25	− 5
Succinic	−15	−50
β-Methylglutaric	−45	−65
Adipic	−10	−30
ββ-Dimethylglutaric	+20	+10
trans-Caronic	+10	−25
Glutaric	−55	−80
β-*iso*Propylglutaric	−40	−50
DL-βγ-Diphenyladipic	−70	−60

For succinic acid, agreement with our ΔC_p for the second ionisation is good, but for the first ionisation it is poor. In view of this fact, and the fact that the other results give values of ΔC_p

which vary over a wider range than the data for ΔC_p for any other acids in the literature, it is perhaps reasonable to suggest that their data are not sufficiently accurate for a discussion of the thermodynamics of the ionisation of dibasic acids. Soper, (private communication) has pointed out that errors in E.M.F. of 1 millivolt would be sufficient to change the sign of ΔC_p for ββ-dimethylglutaric acid, for example, to make it about — 30 cals. per degree. The possibility of such errors arising from small errors in E.M.F. work emphasises the value of calorimetric work in this field. Even the uncertainty in the dilution correction is unlikely to introduce uncertainties as great as those obviously present in thermodynamic functions derived from all but the most precise E.M.F. work.

Consideration of the values obtained from our result shows that for the first ionisation, ΔC_p is quite normal compared with ΔC_p values found for other fatty acids (cf. Part V; Everett and Wynne-Jones, *loc. cit.*; Harned and Owen, *op. cit.*), but that ΔS is significantly less numerically than that for unsubstituted fatty acids except formic acid. This result is as might be expected, for Magee, Ri, and Eyring (*J. Chem. Physics*, 1941, **9**, 419) have already pointed out that the more polar an acid the smaller the entropy loss on ionisation, because more orientation of water molecules might be expected round a polar than round a non-polar solute. For the second ionisation ΔC_p and ΔS are comparable with those for oxalic, but both rather less numerically than those for malonic acid (cf. Harned and Owen, *op. cit.*). In view of the uncertainties in the results, the significance of the difference is not certain, and an attempt to explain it at this stage would be premature.

Kirkwood and Westheimer (*loc. cit.*) have stated that their theory does not provide a satisfactory explanation for the temperature dependence of the electrostatic effect of substituents. In their amplification of this statement, Wynne-Jones and Rushbrooke (*loc. cit.*) used Jones and Soper's data for the temperature variation of the dissociation constants of the dibasic dicarboxylic acids, and various data for aliphatic amino-acids. Westheimer and Kirkwood (*loc. cit.*) have since pointed out that the use by Wynne-Jones and Rushbrooke of the latter data is inadmissible from a theoretical point of view, and our analysis of the former data casts some doubt on their suitability for detailed discussion. It is therefore of interest to consider our results in the light of the electrostatic theory of substituent effect.

The simple Bjerrum theory (*Z. physikal. Chem.*, 1923, **106**, 219) to which the Kirkwood–Westheimer treatment of a dibasic acid reduces as the length between the ionising centres becomes great, gives a value for the interprotonic distance of succinic acid of 3·65 A., which is not very much too small. For succinic acid, Westheimer and Shookhoof (*loc. cit.*) give 5·75 A. as the interprotonic distance obtained by applying the Kirkwood–Westheimer theory to Jones and Soper's value for ΔpK at 25°, 6·66 A. as the maximum interprotonic distance calculated on the basis of accepted valency angles and bond-lengths, and 4·66 A. as the root mean square separation of the protons calculated on the basis of free rotation according to Eyring (*Physical Rev.*, 1932, **39**, 746). Levi (Thesis, Oxford, 1941) has pointed out that the Bjerrum theory gives for the difference between the first and the second heats of ionisation

$$\Delta H_1 - \Delta H_2 = -\frac{e^2N}{a} \cdot \frac{1}{\varepsilon}\left(1 + \frac{T}{\varepsilon}\frac{\partial \varepsilon}{\partial T}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where a is the distance between the ionising centres and the other symbols have their usual significance. Taking a as 5 A., we have that $\Delta H_1 - \Delta H_2$ is about 200 cals. at 0°. Smaller values of a give larger values of $\Delta H_1 - \Delta H_2$. The experimental value of ΔH_1 is almost equal to that of ΔH_2 at 0°, and to secure even approximate agreement with experiment, a fairly large value of a would be necessary.

Differentiating again, we have for the difference in heat capacity changes for the successive stages of ionisation :

$$\Delta C_{p_1} - \Delta C_{p_2} = \frac{Ne^2}{a} \cdot T \cdot \frac{\partial^2}{\partial T^2}\left(\frac{1}{\varepsilon}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The value for succinic acid obtained from this research is about 20 cals. per degree which would require an interprotonic distance (a) of 1 A. Thus we find that in order to fit $\Delta H_1 - \Delta H_2$ at low temperatures, we must use a larger value of a than is physically plausible, whereas to fit its temperature dependence, we must use an impossibly small value of a. This means, of course, that for any given reasonable value of a there is a temperature at which the Bjerrum expression gives the correct value of $\Delta H_1 - \Delta H_2$, but this can hardly be regarded as satisfactory agreement with experiment, although it emphasises the need to take ΔC_p into account.

If the approximations introduced into the Kirkwood–Westheimer theory by Wynne-Jones

and Rushbrooke are accepted, the expression for the difference in heat capacity change is equivalent to the right-hand side of equation (2) multiplied by a factor f, where $f < 1$, and is probably about 0·7.* This refinement of the Bjerrum theory is therefore seen to exaggerate rather than to diminish the discrepancy between theory and experiment for changes in heat capacity (cf. Westheimer and Kirkwood, *loc. cit.*, p. 85).

Thanks are expressed to the Explosives Division of Imperial Chemical Industries Ltd., who made it possible for one of us (T. L. C.) to take part in this work, and to the Royal Society for a grant which defrayed the cost of part of the apparatus used.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 18th*, 1947.]

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202. *Stilbenecarboxylic Acids.*

By F. BELL and D. H. WARING.

The preparation of the undermentioned stilbenecarboxylic acids is described:
Monocarboxylic: 3- and 4- (4 methods).
Dicarboxylic: α : 4, α : 4′, 4 : 4′ (3 methods).
Tricarboxylic: α : 4 : 4′.
By means of 10% potassium hydroxide–ethylene glycol solution, cyanides resistant to the standard processes are readily hydrolysed.

ALTHOUGH stilbenecarboxylic acids are desirable intermediates for many purposes, until recently only the 2- and 2 : 2′-acids had been described, and these were obtained by rather indirect processes (Gabriel and Posner, *Ber.*, 1894, **27**, 2503; Ruggli and Meyer, *Helv. Chim. Acta*, 1922, **5**, 28). More recently Hager, van Arendouk, and Shoule (*J. Amer. Chem. Soc.*, 1944, **66**, 1982) have described the preparation of stilbene-2 : 4′- and -4 : 4′-dicarboxylic acids from the corresponding cyanides, although the hydrolysis presented considerable difficulty.

Three general routes are available for stilbenecarboxylic acids, *viz.*, condensation of the appropriate phenylacetic acid or benzyl cyanide with a benzaldehyde, (ii) coupling of a diazotised aminobenzoic acid with cinnamic acid according to the method of Meerwein, Büchner, and van Emster (*J. pr. Chem.*, 1939, **152**, 237), or (iii) from the nitrostilbene *via* the amine and cyanide. Pfeiffer, Behr, Kübler, and Rüping (*ibid.*, 1929, **121**, 85) have described the preparation of α : 4-dicyanostilbene from *p*-cyanobenzyl cyanide and benzaldehyde. In a similar way α : 4 : 4′-*tricyanostilbene* was prepared from *p*-cyanobenzyl cyanide and *p*-cyanobenzaldehyde, α : 4′-*dicyanostilbene* from benzyl cyanide and *p*-cyanobenzaldehyde, 4 : 4′-dicyanostilbene from *p*-cyanophenylacetic acid and *p*-cyanobenzaldehyde, and 4-cyanostilbene from *p*-cyanophenylacetic acid and benzaldehyde and, also, from phenylacetic acid and *p*-cyanobenzaldehyde. Most of these cyanides were resistant to hydrolysis by the usual methods (cf. Fosdick and Urbach, *J. Amer. Chem. Soc.*, 1947, **69**, 504), but it was found that they could all be converted easily into the corresponding acids by boiling them with a 10% solution of potassium hydroxide in ethylene glycol. The resultant *stilbene*-α : 4- and -α : 4′-*dicarboxylic acids* were converted into *stilbene*-4-*carboxylic acid* by heating them with quinoline and basic copper carbonate (Bergmann and Schapiro, *J. Org. Chem.*, 1947, **12**, 57); similarly the α : 4 : 4′-*tricarboxylic acid* was converted into stilbene-4 : 4′-dicarboxylic acid.

Meerwein's method (*loc. cit.*) applied to *p*-aminobenzoic acid provided a much more satisfactory method of preparation of stilbene-4-carboxylic acid. Similarly, from diazotised *m*-aminobenzoic acid, *stilbene*-3-*carboxylic acid* was obtained in good yield. It was not found possible, however, to prepare stilbene-2-carboxylic acid by a similar reaction from anthranilic acid.

4 : 4′-Dicyanostilbene has been prepared from dibenzyl by Bance, Barber, and Woolman (*J.*, 1943, 1). This was found to be a much more economical method than that of Lamb and White (*J.*, 1939, 1256). From this dicyano-compound stilbene-4 : 4′-dicarboxylic acid was obtained more conveniently than described above.

* It is noteworthy that there is a discrepancy between our evaluation of $\Delta C_{p_1} - \Delta C_{p_2}$ and that in the paper of Wynne-Jones and Rushbrooke. In the first place an arithmetical error makes their value too small by a factor of 2. Furthermore, to represent the temperature variation of the dielectric constant of water they choose an equation used by Everett and Wynne-Jones (*loc. cit.*) to represent Kockel's data (*Ann. Physik*, 1925, **87**, 417); this equation, which gives a value of $\Delta C_{p_1} - \Delta C_{p_2}$ about two-fifths of that calculated here, does not agree with the recent data of Wyman and Ingalls (*J. Amer. Chem. Soc.*, 1398, **60**, 1182) whose results we have used.

Experimental.

α : 4-Dicyanostilbene, from *p*-cyanobenzyl cyanide and benzaldehyde, recrystallised from alcohol in plates, m. p. 145° (Pfeiffer, Behr, Kübler, and Rüping, *loc. cit.*, give needles, m. p. 147°). Heated at 140° for 1½ hours with a mixture of equal volumes of sulphuric acid, acetic acid, and water, it furnished *α-cyanostilbene-4-carboxylic acid* together with other compounds from which it was freed with considerable difficulty. This acid was best prepared by hydrolysis with hydrogen chloride in ethyl alcohol solution and saponification of the resultant ester. It formed long hair-like needles, m. p. 245° (Found : N, 6·0; equiv., 249. $C_{16}H_{11}O_2N$ requires N, 5·6%; equiv., 251), and dissolved in sulphuric acid at 100° to give a bright crimson solution from which an orange-yellow indonesulphonic acid was precipitated by water.

Stilbene-α : 4-dicarboxylic Acid.—(*a*) α-Cyanostilbene-4-carboxylic acid (1·0 g.) was hydrolysed by heating it for 3 hours under reflux at 140—160° with 10 c.c. of 10% potassium hydroxide–ethylene glycol solution. The resultant *stilbene-α : 4-dicarboxylic acid* crystallised in needles from aqueous alcohol, m. p. 225° (Found : equiv., 133. $C_{16}H_{12}O_4$ requires equiv., 134).

(*b*) Homoterephthalic acid (9·0 g.), mixed with benzaldehyde (5·5 g.) and piperidine (5 drops), was heated 3 hours at 150—160°. The deep red product was crystallised from glacial acetic acid and then from aqueous alcohol; yield, 5·4 g.; m. p. 225°.

Decarboxylation. Stilbene-α : 4-dicarboxylic acid (2·0 g.) was heated with quinoline (20 c.c.) and basic copper carbonate (2·0 g.). Reaction began at 145° and was apparently complete in 45 minutes. Heating was continued for a further 15 minutes, and the quinoline removed by steam. Acidification of the residue yielded stilbene-4-carboxylic acid, m. p. 245°.

α : 4′-*Dicyanostilbene.*—*p*-Cyanobenzaldehyde (2·0 g.), mixed with benzyl cyanide (2·0 g.) and piperidine (5 drops), was heated at 150° for 1 hour. The product, which solidified on standing, was recrystallised from ethyl alcohol. α : 4′-*Dicyanostilbene* forms fine needles, m. p. 172° (Found : N, 11·9. $C_{16}H_{10}N_2$ requires N, 12·2%).

Stilbene-α : 4′-dicarboxylic Acid.—α : 4′-Dicyanostilbene (1·0 g.) was heated with 10% potassium hydroxide–ethylene glycol (10 c.c.) solution for 4 hours. The resultant *stilbene-α : 4′-dicarboxylic acid* crystallised from alcohol; m. p. 293° (Found : equiv., 132. $C_{16}H_{12}O_4$ requires equiv., 134). This acid was readily decarboxylated to stilbene-4-carboxylic acid by the quinoline–copper carbonate method.

α : 4 : 4′-*Tricyanostilbene.*—*p*-Cyanobenzaldehyde (5·2 g.) was heated with *p*-cyanobenzyl cyanide (5·6 g.) at 140°, and piperidine (3 drops) was added to the molten mixture, which immediately solidified. The red mass was recrystallised from piperidine, giving α : 4 : 4′-*tricyanostilbene* as pale yellow needles, m. p. 302—303°; yield, 6·5 g. (Found : C, 79·8; H, 3·7; N, 16·8. $C_{17}H_9N_3$ requires C, 80·0; H, 3·5; N, 16·5%).

α-Cyanostilbene-4 : 4′-dicarboxylic acid was obtained by heating the tricyano-compound with sulphuric acid–acetic acid for 8 hours at 140°, and also by alkaline hydrolysis of ethyl α-cyanostilbene-4 : 4′-dicarboxylate (obtained by 18 hours' alcoholysis of the tricyano-compound with hydrogen chloride and ethyl alcohol). It formed a white powder insoluble in the usual organic solvents (Found : N, 4·67; equiv., 147·1. $C_{17}H_{11}O_4N$ requires N, 4·77%; equiv., 146·5).

Stilbene-α : 4 : 4′-tricarboxylic acid, obtained by heating α-cyanostilbene-4 : 4′-dicarboxylic acid (1·5 g.) at 150—160° for 4 hours with 10% potassium hydroxide–ethylene glycol solution (10 c.c.), crystallised from acetic acid as small plates, m. p. 286—288° (Found : equiv. 103. $C_{17}H_{12}O_6$ requires equiv., 104). It was readily decarboxylated to stilbene-4 : 4′-dicarboxylic acid.

Stilbene-4 : 4′-dicarboxylic Acid.—4 : 4′-Dicyanostilbene (5·0 g.) was heated at 160—170° with potassium hydroxide–ethylene glycol solution (50 c.c.) until evolution of ammonia was complete (3 hours), poured into water, and the free acid liberated with dilute sulphuric acid. The liquid containing the gelatinous precipitate was left on a hot plate for several hours to facilitate filtration. Stilbene-4 : 4′-dicarboxylic acid (Found : equiv., 135. Calc. : equiv., 134) is a white amorphous powder insoluble in the usual organic solvents, including nitrobenzene, dioxan, and phenol, but easily converted into stilbene by heating with lime. Stilbene-2 : 4′-dicarboxylic acid, m. p. 296°, was obtained in the same way from the readily-available 2 : 4′-dicyanostilbene (Bance, Barber, and Woolman, *loc. cit.*).

Stilbene-4 : 4′-dicarboxylic Chloride.—Stilbene-4 : 4′-dicarboxylic acid (2·0 g.) was heated for 12 hours with thionyl chloride (10 c.c.). Excess of thionyl chloride was evaporated off and the last traces removed over soda-lime in vacuum desiccator. The residue was crystallised twice from benzene–light petroleum, and the *chloride* formed a white powder, m. p. 223—224° (Found : Cl, 23·4. $C_{16}H_{10}O_2Cl_2$ requires Cl, 23·2%).

Anilide of Stilbene-4 : 4′-dicarboxylic Acid.—Stilbene-4 : 4′-dicarboxylic chloride (1·0 g.) was heated for several minutes with a few c.c. of aniline, and the *anilide* precipitated by dilute hydrochloric acid. It crystallised from nitrobenzene in small hair-like needles, m. p. 316—317° (Found : N, 6·66. $C_{28}H_{22}O_2N_2$ requires N, 6·7%).

4-Cyanostilbene was prepared by condensation of equimolecular proportions of *p*-cyanophenylacetic acid and benzaldehyde or phenylacetic acid and *p*-cyanobenzaldehyde at 160—170° in the presence of a few c.c. of piperidine; it formed fine needles, m. p. 115°, from alcohol or 80% acetic acid.

Stilbene-4-carboxylic Acid.—(a) *Hydrolysis of 4-cyanostilbene.* 4-Cyanostilbene (2·5 g.) was heated at 160—170° with 10% potassium hydroxide–ethylene glycol solution until evolution of ammonia was complete (2 hours). Yield, 2·6 g.; m. p. 245°.

(b) *Meerwein reaction.* The hydrochloride of 4-aminobenzoic acid (25 g.) was suspended in a mixture of concentrated hydrochloric acid (25 c.c.) and water (40 c.c.), and diazotised with a solution of sodium nitrite (11 g.) in water (20 c.c.). The diazo-solution was filtered, and sodium acetate (35 g.) stirred in. When solution was complete, cinnamic acid (22 g.) in acetone (200 c.c.) was added and the ice-bath removed. 5 Minutes later, cupric chloride (6·5 g.) dissolved in water (20 c.c.) was added. The mixture was well stirred and the temperature allowed to rise slowly to 17° during 1 hour. Sitrring was then continued for a further 2 hours at 30°. The acetone was removed by steam, and the *stilbene-4-carboxylic acid* which had separated was recrystallised twice from glacial acetic acid, yielding a fine crystalline powder, m. p. 244—245° (yield 60%) (Found : equiv., 223. $C_{15}H_{12}O_2$ requires equiv., 224).

Stilbene-3-carboxylic Acid.—Procedure and quantities were the same as for the isomeric 4-acid,

except that after 1 hour's stirring to room temperature the mixture was then stirred for 3 hours at 23—25°. After this time evolution of gas was complete, and two layers had formed. The upper layer was a dark green oil, and the lower layer a bright green water–acetone mixture.

The acetone was removed by steam, and the oily layer, which solidified on cooling, was recrystallised twice from glacial acetic acid. Further recrystallisation from benzene or aqueous alcohol gave *stilbene-3-carboxylic acid* as small, fine crystals, m. p. 194—195° (Found: equiv., 225. $C_{15}H_{12}O_2$ requires equiv., 224).

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203. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXV. The Phthalazine Reaction with Bases not containing a Nitro-group. Derivatives of 2′-Chlorobenzene-2-naphthol-1-diazosulphonate.*

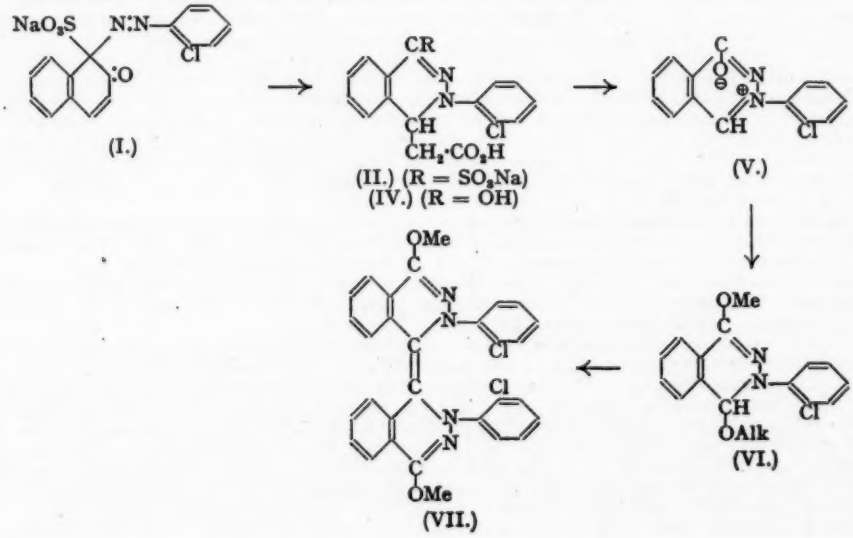
By C. I. BRODRICK, A. T. PETERS, and (the late) F. M. ROWE.

This paper confirms that the presence of a nitro-group is not essential for the conversion of aryl-2-naphthol-1-diazosulphonates into phthalazine and phthalazone derivatives (cf. Part XXIV, this vol., p. 597). Thus, the diazosulphonate derived from *o*-chloroaniline is convertible into *sodium hydrogen* 3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (II), which possesses the expected properties. 2′-*Chloro*-3-*phenylphthalaz*-1-*one* and 2′-*chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* are isomerised to 2′-*chloro*-3-*phenylphthalaz*-4-*one* and its 1-*methyl* derivative, respectively, and the constitutions of the two last-named compounds are confirmed by synthesis.

2′-CHLOROBENZENE-2-NAPHTHOL-1-DIAZOSULPHONATE was converted by aqueous sodium carbonate into sodium 1-(2′-chlorobenzeneazo)-β-naphthaquinone-1-sulphonate (I), which with cold aqueous sodium hydroxide gave 66·2% of (II). This yield is similar to that (69·8%) observed in the case of the 2′-nitro-analogue, and there was no increase in yield on prolonged reaction of (I) with sodium hydroxide. Sodium benzaldehyde-2′-chlorophenylhydrazone-ω-sulphonate-2-β-acrylic acid (III) could not be detected by the restricted action (*e.g.*, 1 minute) of sodium hydroxide on (I), whereas the 2′-nitro-analogue of (III) was formed in 81·8% yield (cf. *J.*, 1935, 1796).

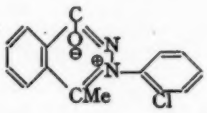
1-*Hydroxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (IV), which was formed when the sodium salt (II) was boiled with dilute hydrochloric acid, was converted by boiling aqueous sulphuric acid, or by a mixture of sulphuric and acetic acid, or by fuming hydrochloric acid (*d* 1·19) at 180°, into 2′-*chloro*-3-*phenylphthalaz*-1-*one* (V) (which forms a *picrate*).

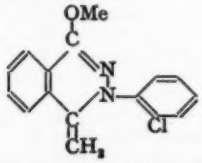
The methylation product of (V) combined with methyl or ethyl alcohol to give 1 : 4-*dimethoxy*- or 1-*methoxy*-4-*ethoxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine* [as (VI)], respectively (cf. *J.*, 1928, 2554).



Usually, such derivatives are converted by heating at 100—140° into the corresponding 4-keto-1-methoxy-derivatives (*J.*, 1928, 2554), or, as in the case of the 2′-nitro-analogues, are decomposed by heat (cf. *J.*, 1935, 1796). In the present case, however, compounds (VI) lost the respective alcohol at 140° and gave (VII), formed by the joining of two molecules at C_4. The constitution of the phthalazone (V) was confirmed by Clemmensen reduction to 1-*keto*-3-(2′-*chlorophenyl*)*tetrahydrophthalazine* and thence to 2′-*chloro*-N-*phenylphthalimidine*. On heating with aqueous hydrochloric acid (1 : 8) in a sealed tube at 180° for 28 hours, compound (V) was partly isomerised to give 30% of 2′-*chloro*-3-*phenylphthalaz*-4-*one*, which did not form a picrate and could not be methylated. The phthalaz-4-one was identical with a synthetic specimen prepared from *o*-phthalaldehydic acid and *o*-chlorophenylhydrazine, followed by cyclisation of the resulting o-*carboxybenzaldehyde* 2′-*chlorophenylhydrazone*. When the hydroxy-compound (IV) was oxidised with cold acid dichromate or cold nitric acid, 2′-*chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (VIII) was formed; this yielded a picrate and was readily methylated to 1-*methoxy*-3-(2′-*chlorophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (IX).

(VIII.)





(IX.)

This reactive methylene derivative (IX) formed a perchlorate, and with 2 : 4-dinitrochlorobenzene in boiling alcohol in presence of potassium acetate gave 1-*methoxy*-3-(2′-*chlorophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*. The constitution of the phthalazone (VIII) was further confirmed by reduction with sodium dithionite (hydrosulphite) or by the Clemmensen procedure to 1-*keto*-3-(2′-*chlorophenyl*)-4-*methyltetrahydrophthalazine*, and by its partial isomerisation by aqueous hydrochloric acid (1 : 8) at 180° to give 13·3% of 2′-*chloro*-3-*phenyl*-1-*methylphthalaz*-4-*one*. This compound was synthesised from acetophenone-*o*-carboxylic acid and *o*-chlorophenylhydrazine, followed by cyclisation of the resulting o-*carboxyacetophenone* 2′-*chlorophenylhydrazone* with cold concentrated sulphuric acid.

Permanganate oxidation of the hydroxy-compound (IV) gave 1 : 4-*diketo*-3-(2′-*chlorophenyl*)*tetrahydrophthalazine*, which was converted through its silver salt and methyl iodide into 4-*keto*-1-*methoxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*, also formed by boiling the methylene compound (IX) with *p*-nitrosodimethylaniline in alcohol.

Experimental.

Sodium Hydrogen 3-(2′-*Chlorophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (II).—*o*-Chlorobenzenediazonium chloride, prepared from 25·5 g. of *o*-chloroaniline, was well stirred during the addition of 50% sodium β-naphthol-1-sulphonate (100 g.) in water (240 c.c.) at 0°. The yellow precipitate of 2′-chlorobenzene-2-naphthol-1-diazosulphonate was collected, washed with brine, and pasted with sodium carbonate (50 g.) in water (200 c.c.); the orange sodium 1-(2′-chlorobenzeneazo)-β-naphthaquinone-1-sulphonate was formed after grinding for 15 minutes, and to it was added sodium hydroxide (50 g.) in water (120 c.c.). After 2 hours at <5°, the mixture was acidified with hydrochloric acid, made just alkaline with sodium carbonate, 2′-chlorobenzeneazo-β-naphthol (3 g.; 5·3%) filtered off, and the filtrate made faintly acid. Addition of sodium chloride precipitated a resinous black mass, which was purified by dissolution in alcohol and addition of ether. The resulting pale brown crystals of the *sodium hydrogen* salt were dried at 140° (53·4 g.; 66·2%) (Found: S, 7·1. $C_{16}H_{12}O_5N_2ClSNa$ requires S, 7·95. $C_{16}H_{12}O_5N_2ClSNa,C_2H_6O$ requires S, 7·1%). At 150°, some decomposition occurred and the product became progressively darker and decomposed at 235—240°.

1-*Hydroxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (IV).—The above sodium salt (II) (7 g.) was boiled with water (500 c.c.), and hydrochloric acid (40 c.c.) added slowly during 2 hours; the separated *acid* (IV) crystallised from aqueous acetic acid in colourless needles, m. p. 224—225° (shrinks from 210°) (4·6 g.; 83·6%) (Found: C, 60·6; H, 4·1; N, 9·3; Cl, 11·2. $C_{16}H_{13}O_3N_2Cl$ requires C, 60·7; H, 4·1; N, 8·85; Cl, 11·2%). For preparation in quantity, it was found convenient to proceed with the hydrolysis without prior separation of the sodium salt.

The *methyl* ester crystallised from methyl alcohol in colourless, hexagonal plates, m. p. 141—142° (Found: N, 8·8; Cl, 10·8. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5; Cl, 10·7%). The *ethyl* ester formed colourless prisms (alcohol), m. p. 132—133° (Found: N, 8·6. $C_{18}H_{17}O_3N_2Cl$ requires N, 8·1%).

With boiling acetic anhydride–pyridine (15 : 1) for 70 hours, or with phosphorus trichloride in boiling toluene for 8 hours, the hydroxy-compound (IV) gave the internal *anhydride*, which crystallised from nitrobenzene in colourless needles, darkening at 300° and decomposing at > 340° (Found: C, 64·2; H, 3·7; N, 9·8; Cl, 11·4. $C_{16}H_{11}O_2N_2Cl$ requires C, 64·3; H, 3·7; N, 9·4; Cl, 11·9%), reconverted into the acid (IV) on warming with concentrated sulphuric acid.

The *N*-methyl ether of (IV), *viz.*, 1-*keto*-3-(2′-*chlorophenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, crystallised from aqueous acetic acid in colourless rhombs, m. p. 180—181° (Found: N, 8·7. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5%).

2′-Chloro-3-phenylphthalaz-1-one (V).—The hydroxy-compound (IV) (10 g.) was refluxed with concentrated sulphuric acid (40 c.c.) and water (50 c.c.) for 3 hours, and the mixture added to ice. The precipitated sulphate was basified with aqueous ammonia; the *phthalazone* crystallised from aqueous alcohol in almost colourless prisms, m. p. 202—203° (5·6 g.; 68·2%) (Found: C, 65·8; H, 3·6; N, 11·0; Cl, 13·6. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9; Cl, 13·8%). It was also obtained in 69% yield by boiling (IV) with sulphuric acid and acetic acid (1 : 1 by vol.) for 15 minutes, or in 35·4% yield by heating (IV) with fuming hydrochloric acid (*d* 1·19) in a sealed tube at 180° for 4 hours; in the latter case, some unidentified substance, which crystallised from alcohol in fine colourless needles, m. p. 165°, was also isolated.

2′-Chloro-3-phenylphthalaz-1-one picrate crystallised from alcohol in bright yellow rectangular prisms, m. p. 233—234° (Found: N, 14·4. $C_{20}H_{12}O_8N_5Cl$ requires N, 14·4%).

Methylation of (V).—3 G. of (V) were heated with methyl sulphate (15 g.) at 70° for 2 hours, poured into water, and the mixture made alkaline with sodium carbonate; the *methoxy*-derivative [as (VI)] crystallised from methyl alcohol in colourless hexagonal prisms, m. p. 78° (Found: N, 9·0. $C_{16}H_{13}O_2N_2Cl$ requires N, 9·3%), or from ethyl alcohol in similar prisms, m. p. 86° (Found: N, 8·7. $C_{17}H_{15}O_2N_2Cl$ requires N, 8·9%), which are probably 1 : 4-*dimethoxy*- and 1-*methoxy*-4-*ethoxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine* respectively. On being heated at 110° for 4 hours and then at 140° for 1 hour, each compound lost the respective alcohol and yielded the same *substance* (VII), which crystallised from nitrobenzene in bright yellow cubes, m. p. 239° (decomp.) [Found: C, 66·7; H, 4·1; N, 9·9; Cl, 12·75. $(C_{15}H_{11}ON_2Cl)_2$ requires C, 66·55; H, 4·1; N, 10·35; Cl, 13·1%].

1-*Keto*-3-(2′-*chlorophenyl*)*tetrahydrophthalazine*.—2′-Chloro-3-phenylphthalaz-1-one (2 g.) was heated with hydrochloric acid (80 c.c.), water (80 c.c.), and zinc amalgam (120 g.) at 70—80° for 1 hour; the *keto*-compound crystallised from alcohol in colourless needles, m. p. 216—218° (1 g.; 49·6%) (Found: C, 65·6; H, 4·2; N, 10·8. $C_{14}H_{11}ON_2Cl$ requires C, 65·0; H, 4·3; N, 10·8%).

2′-Chloro-N-phenylphthalimidine.—2′-Chloro-3-phenylphthalaz-1-one (1 g.) was boiled with hydrochloric acid (40 c.c.), water (40 c.c.), alcohol (30 c.c.), and zinc amalgam (70 g.) for 4 hours; no solid separated, but, on pouring on ice, the *phthalimidine* was precipitated; it crystallised from alcohol in colourless prismatic needles, m. p. 124° (0·8 g.; 84·2%) (Found: C, 68·1; H, 4·1; N, 5·9; Cl, 14·2. $C_{14}H_{10}ONCl$ requires C, 69·0; H, 4·1; N, 5·75; Cl, 14·6%). It was also obtained in 85% yield by a similar reduction of 1-keto-3-(2′-chlorophenyl)tetrahydrophthalazine.

Conversion of 2′-Chloro-3-phenylphthalaz-1-one into 2′-Chloro-3-phenylphthalaz-4-one.—The phthalaz-1-one (3 g.) and aqueous hydrochloric acid (1 : 8; 36 c.c.) in a sealed tube at 180° for 28 hours gave *2′-chloro-3-phenylphthalaz-4-one* (0·9 g.; 30%), which crystallised from acetic acid in colourless prisms, m. p. 126—127° (Found: C, 65·6; H, 3·6; N, 11·2. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9%), identical with a synthetic specimen.

Synthesis of 2′-Chloro-3-phenylphthalaz-4-one.—*o*-Phthalaldehydic acid (1·8 g.) and *o*-chlorophenylhydrazine (1·7 g.) in boiling alcohol (25 c.c.) for 20 minutes gave *o-carboxybenzaldehyde 2′-chlorophenylhydrazone*, which crystallised from alcohol in yellow prismatic needles, m. p. 175° (3 g.; 91%) (Found: N, 10·5. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2%), converted by cold concentrated sulphuric acid in 12 hours or by boiling with acetic acid for 30 minutes into 92% of 2′-chloro-3-phenylphthalaz-4-one, m. p. 127°, identical with that prepared above. With boiling acetic anhydride, the above hydrazone, m. p. 175°, was converted into *o-carboxybenzaldehyde α-acetylhydrazone* (lactone form), which crystallised from alcohol or acetic acid in colourless hexagonal plates, m. p. 169° (Found: C, 61·1; H, 4·5; N, 8·9; Cl, 11·2. $C_{16}H_{13}O_3N_2Cl$ requires C, 60·7; H, 4·1; N, 8·85; Cl, 11·2%).

2′-Chloro-3-phenyl-4-methylphthalaz-1-one (VIII).—(*a*) The hydroxy-compound (IV) (20 g.) in concentrated sulphuric acid (180 c.c.) was poured on ice (400 g.), and the fine suspension stirred during addition of potassium dichromate (9 g.) (30 minutes) at 5°. After being left overnight at room temperature, the separated sulphate was collected and basified with aqueous sodium hydroxide; it crystallised from aqueous alcohol in fine colourless needles, m. p. 253—255° (darken at 240°) (13·5 g.; 79%) (Found: C, 66·8; H, 4·2; N, 10·0; Cl, 13·1. $C_{15}H_{11}ON_2Cl$ requires C, 66·55; H, 4·1; N, 10·35; Cl, 13·1%). The *picrate* crystallised from alcohol in golden-yellow prisms, m. p. 199—200° (decomp.) (Found: N, 14·0. $C_{21}H_{14}O_8N_5Cl$ requires N, 14·1%).

(*b*) The hydroxy-compound (IV) (10 g.) was added slowly to nitric acid (*d* 1·5; 60 c.c.) at below 5°, and after 1 hour, the mixture was added to ice to give the nitrate of 2′-chloro-3-phenyl-4-methylphthalaz-1-one as colourless prisms (methyl alcohol), m. p. 253—255° (decomp.); conversion into the base was effected by cold aqueous sodium carbonate (yield, 7·2 g.; 84·3%).

1-*Methoxy*-3-(2′-*chlorophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (IX).—2′-Chloro-3-phenyl-4-methylphthalaz-1-one (3 g.) and methyl sulphate (12 g.) at 70—80° for 2 hours gave, on addition to water, the *methylene* base, which crystallised from methyl alcohol in orange-brown diamond-shaped prisms, or in small yellow prisms, m. p. 119° (2·4 g.; 76·2%) (Found: C, 67·4; H, 4·6; N, 10·0; Cl, 12·4. $C_{16}H_{13}ON_2Cl$ requires C, 67·5; H, 4·6; N, 9·8; Cl, 12·5%). The *perchlorate* crystallised from alcohol containing a little perchloric acid in colourless prismatic needles, m. p. 202° (Found: N, 7·5; Cl, 18·4. $C_{16}H_{14}O_5N_2Cl_2$ requires N, 7·3; Cl, 18·4%).

1-*Methoxy*-3-(2′-*chlorophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*.—This was obtained by boiling the above methylene compound (IX) (1 g.) with chloro-2 : 4-dinitrobenzene (1 g.) in alcohol (60 c.c.) and potassium acetate (1·5 g.) for 5 hours. It crystallised from acetic anhydride in black prismatic needles with a bronze lustre, m. p. 186° (0·46 g.; 58·1%) (Found: C, 59·2; H, 3·4; Cl, 8·0. $C_{22}H_{15}O_5N_4Cl$ requires C, 58·6; H, 3·3; Cl, 7·9%).

1-*Keto*-3-(2′-*chlorophenyl*)-4-*methyltetrahydrophthalazine*.—2′-Chloro-3-phenyl-4-methylphthalaz-1-one (1 g.) was reduced with alkaline sodium dithionite (9 g.) to give the *keto*-compound, which crystallised from alcohol in colourless prisms, m. p. 199—200° (0·85 g.; 84·4%) (Found: C, 66·0; H, 4·8; N, 10·3; Cl, 12·4. $C_{15}H_{13}ON_2Cl$ requires C, 66·05; H, 4·8; N, 10·3; Cl, 13·0%). The same compound was obtained by heating the above phthalaz-1-one (2 g.) with boiling hydrochloric acid (70 c.c.), water (40 c.c.), and zinc amalgam (90 g.) at 70—80° for 4 hours (1·9 g.; 94%), and prolonged reduction failed to yield 2′-chloro-*N*-phenyl-3-methylphthalimidine.

Conversion of 2'-Chloro-3-phenyl-4-methylphthalaz-1-one into the Isomeric 1-Methylphthalaz-4-one.—This was effected by heating 1 g. with aqueous hydrochloric acid (1 : 8; 12 c.c.) at 180° for 28 hours. *2'-Chloro-3-phenyl-1-methylphthalaz-4-one* crystallised from acetic acid in colourless prismatic needles, m. p. 147° (0·2 g.; 13·3%) (Found: C, 66·8; H, 4·0; Cl, 12·6. $C_{15}H_{11}ON_2Cl$ requires C, 66·55; H, 4·1; Cl, 13·1%).

Synthesis of 2'-Chloro-3-phenyl-1-methylphthalaz-4-one.—Acetophenone-*o*-carboxylic acid (1·4 g.) and *o*-chlorophenylhydrazine (1·2 g.) in alcohol at room temperature gave an immediate precipitate of *o-carboxyacetophenone 2'-chlorophenylhydrazone*, which crystallised from alcohol in fine, pale yellow needles, m. p. 132° (1·05 g.; 85·3%) (Found: N, 9·5. $C_{15}H_{12}O_2N_2Cl$ requires N, 9·7%). Cold concentrated sulphuric acid in 12 hours caused 97% cyclisation to 2'-chloro-3-phenyl-1-methylphthalaz-4-one, m. p. 147°, identical with that obtained above.

1 : 4-*Diketo*-3-(2'-*chlorophenyl*)*tetrahydrophthalazine.*—Powdered potassium permanganate (10 g.) was added during 10 minutes to 1-hydroxy-3-(2'-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) suspended in water (200 c.c.) at 80°, and after 30 minutes the mixture was filtered and the filtrate acidified to give the *tetrahydrophthalazine*, which crystallised from aqueous acetic acid in colourless rectangular prisms, m. p. 247—248° (4·2 g.; 48·8%) (Found: C, 61·6; H, 3·1; N, 10·2; Cl, 13·3. $C_{14}H_9O_2N_2Cl$ requires C, 61·6; H, 3·3; N, 10·3; Cl, 13·0%). The silver salt separated when aqueous silver nitrate was added to a solution of the compound in aqueous ammonia.

4-*Keto*-1-*methoxy*-3-(2'-*chlorophenyl*)-3 : 4-*dihydrophthalazine.*—(*a*) The above dry silver salt (1 g.) was refluxed with methyl iodide (0·7 c.c.) in dry toluene (40 c.c.) for 30 minutes, the mixture filtered, and the filtrate evaporated to dryness. On extraction of the residue with methyl alcohol, and cooling, the *methoxy-keto*-compound separated in colourless prisms, m. p. 136—137° (0·1 g.; 26·5%) (Found: C, 62·8; H, 3·9; N, 9·8. $C_{15}H_{11}O_2N_2Cl$ requires C, 62·8; H, 3·8; N, 9·8%).

(*b*) The methylene compound (IX) (0·9 g.) was boiled with *p*-nitrosodimethylaniline (1 g.) in alcohol (40 c.c.) for 3 hours; concentration caused separation of the 1-methoxy-4-keto-compound, which crystallised from methyl alcohol in colourless prisms, m. p. 137° (0·37 g.; 40·8%).

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204. *The Relative Strengths of Some Fatty Acids.*

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Preliminary work on determinations of relative acid strength shows that, among the fatty acids, there are at least six cases of inversion of strength in the temperature range 15—45°. These observations confirm predictions based on the work of Tully and Levi on the heats of neutralisation of the acids concerned. Preliminary data are also given on the strength of trimethylacetic acid.

IN recent years there has been some discussion regarding the validity of using ionisation constants, obtained in aqueous solution at a single temperature, as a basis for the theoretical interpretation of the relative strengths of acids. On the one hand (Hammett, *J. Chem. Physics*, 1936, **4**, 613; Baker, in Baker, Dippy and Page, *J.*, 1937, 1774; Everett and Wynne-Jones, *Trans. Faraday Soc.*, 1939, **35**, 1380; 1941, **37**, 373), it was realised that the way in which acid constants vary with temperature might lead to inversions in relative acid strength, and thus throw doubt on theoretical arguments based on data referring to a single temperature. Against this (Dippy, in Baker, Dippy, and Page, *loc. cit.*; Dippy, *J.*, 1938, 1222; *Chem. Rev.*, 1939, **25**, 151; Dippy and Jenkins, *Trans. Faraday Soc.*, 1941, **37**, 368) it was contended that no examples of inversion had been observed in the range of temperatures examined experimentally. In fact (Everett and Wynne-Jones, *loc. cit.*, 1941) some inversions within the experimental range were known, *e.g.*, among the first dissociation constants of the α-amino-acids; but it might be argued that these represent a special type of ionisation and that this behaviour is not general.

The heats of neutralisation of a series of acids in the temperature range 10—30° have been measured calorimetrically by Tully (Thesis, Oxford, 1939) and Levi (Thesis, Oxford, 1941), and these data, when taken in conjunction with Dippy's values for log $K_{25°}$, suggest that inversions of acid strength should occur in the range 15—45° with the following pairs of fatty acids: acetic and *iso*valeric, propionic and *iso*butyric, propionic and *n*-valeric, propionic and *n*-hexoic.

We have made a direct comparison of the strengths of these pairs of acids by measurements of the e.m.f. of cells of the following type

$$H_2 \;\Big|\; \begin{matrix} 0{\cdot}02\text{N-HA}_1 \\ 0{\cdot}02\text{N-NaA}_1 \end{matrix} \;\Big|\; 0{\cdot}08\text{N-NaCl} \;\Big|\; 3{\cdot}5\text{N-KCl} \;\Big|\; 0{\cdot}08\text{N-NaCl} \;\Big|\; \begin{matrix} 0{\cdot}02\text{N-HA}_2 \\ 0{\cdot}02\text{N-NaA}_2 \end{matrix} \;\Big|\; H_2$$

over a range of temperature. The buffer ratios and the total ionic strengths are identical in the two half-cells, so the total e.m.f. is given by

$$E = (2{\cdot}303\,RT/F)\log_{10} K_{HA_2}/K_{HA_1}$$

the negative electrode being that in the buffer solution containing the weaker acid. The symmetry of this cell, especially when the acids HA_1 and HA_2 are very similar, reduces the overall liquid-junction potential to negligible proportions. Even when the two compartments contain widely different solutions, such as an amine buffer and hydrochloric acid (Everett and Wynne-Jones, *Proc. Roy. Soc.*, 1938, *A*, **169**, 190; 1941, *A*, **177**, 499), the liquid-junction correction is only a few tenths of a millivolt. The reliability of the technique for making the liquid junctions (cf. Unmack and Guggenheim, *Kgl. Dansk Vid. Selsk.*, 1930, **10**, 8) and their stability at various temperatures were checked by making up a completely symmetrical cell containing the same acetate buffer in both half-cells. At 20° the cell had an overall e.m.f. of 0·04 mv. Readings were then taken at 5° intervals up to 50°; the e.m.f. remained steady to ± 0·04 mv. throughout the experiment.

The relative dissociation constant, $K_r = K_{HA_2}/K_{HA_1}$, of a pair of acids is thus readily determined at a given ionic strength. A full examination of this technique will require measurements at a series of buffer concentrations and at several ionic strengths, but it seems unlikely that serious errors will be introduced in the relative constants between 0·10N and infinite dilution. This is confirmed by the agreement between the relative dissociation constants obtained in this work at 25°, and those calculated from Dippy's thermodynamic dissociation constants. Furthermore, Larsson and Adell (*Z. physikal. Chem.*, 1931, *A*, **156**, 352) have shown that for the fatty acids we have examined the activity coefficients at an ionic strength of 0·1N are constant to within about ± 2%.

Experimental.

The acids employed were all purified samples: acetic acid was "AnalaR" grade; propionic was redistilled (b. p. 137·5°/760 mm.); *iso*butyric, redistilled (b. p. 153·4°/760 mm.); *iso*valeric, twice distilled (b. p. 170·6°/722 mm.); *n*-valeric, Kahlbaum; *n*-hexoic redistilled (b. p. 108·3—109·0°/25 mm.) and fractionally crystallised. Trimethylacetic acid was a pure synthetic preparation (b. p. 79°/20 mm.). Buffer solutions were prepared from carefully standardised solutions of the acids, and carbonate-free sodium hydroxide solution; the ionic strength was adjusted by addition of standard sodium chloride solution made from purified salt (Manov, Delollis, and Acree, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 287).

Measurements of e.m.f. were made by means of a Tinsley vernier potentiometer and a recently standardised Weston cell. The e.m.f. cells and hydrogen saturators were similar to those used previously (Everett and Wynne-Jones, *locc. cit.*, 1938 and 1941).

The results are summarised in the table; the e.m.f.s have been corrected for small deviations of the actual buffer ratios from unity. Figures for the pair trimethylacetic–acetic acid are also included; no

HA_1 = Acetic acid; HA_2 = *iso*valeric acid.

Temp.	*E*, mv.	K_r.
5·04°	+2·14	1·093
10·00	+1·26	1·053
15·00	+0·35	1·014
19·97	−0·50	$0·980_5$
25·00	−1·32	0·950
	(cf.	0·952,*
		0·93 †)
30·00	−2·18	0·920

Inversion temp., 17·3°; ΔH_r − 1155 cals./mole; T_m‡ − 10°.

HA_1 = Acetic acid; HA_2 = trimethylacetic acid.

Temp.	*E*, mv.	K_r.
25·00°	−16·61	$0·533_0$
	(cf.	0·508 *)
30·00	−16·91	$0·523_2$
40·00	−18·40	$0·505_6$
50·00	−19·86	0·4899
60·00	−21·41	$0·474_2$

ΔH_r − 655 cals./mole; T_m‡ + 3°.

HA_1 = Propionic acid; HA_2 = *n*-valeric acid.

Temp.	*E*, mv.	K_r.
25·00°	+1·18	1·047
	(cf.	1·034,*
		1·12 †)
30·00	+0·89	1·035
35·00	+0·55	1·021
45·00	−0·03	0·999
50·00	−0·34	0·988
55·00	−0·58	0·980

Inversion temp., 44·4°; ΔH_r − 445 cals./mole; T_m‡ + 7°.

HA_1 = Propionic acid; HA_2 = *n*-hexoic acid.

Temp.	*E*, mv.	K_r.
25·00°	+1·19	1·047
		(cf. 0·990,* 1·03 †)
30·00	+0·087	1·034
35·00	+0·55	1·021
40·00	+0·23	1·009

Inversion temp., 43·3°; ΔH_r − 465 cals./mole; T_m‡ + 7°.

HA_1 = Propionic acid; HA_2 = *iso*butyric acid.

Temp.	*E*, mv.	K_r.
25·00°	+1·21	1·048
		(cf. 1·034,* 1·07 †)
30·00	+0·80	1·031
35·00	+0·40	1·015
40·00	0·00	1·000
45·00	−0·39	0·986
50·00	−0·78	0·978

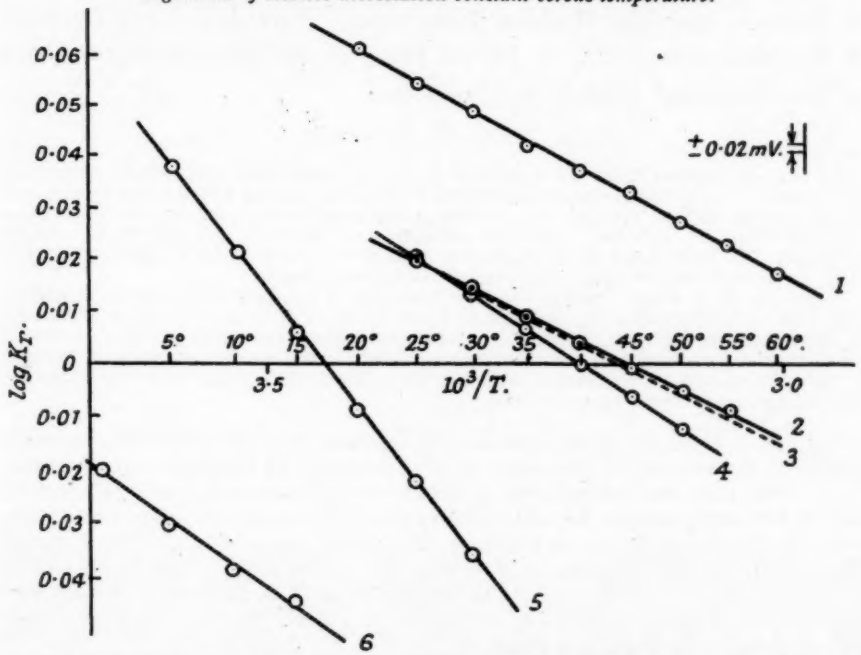
Inversion temp., 40·0°; ΔH_r − 581 cals./mole; T_m‡ + 4°.

* Dippy, *loc. cit.*, 1939. † Franke, *loc. cit.*
‡ Temperature at which log K_2 is a maximum.

inversion point was expected here, but it was of interest to determine the position of the maximum in the log K–T curve of trimethylacetic acid. The table also contains values of K_r calculated from Dippy's thermodynamic constants [taking $K_{acetic} = 1{\cdot}754 \times 10^{-5}$ and $K_{propionic} = 1{\cdot}335 \times 10^{-5}$ (Harned and Ehlers, *J. Amer. Chem. Soc.*, 1933, **55**, 652, 2379)] and from the classical dissociation constants of Franke (*Z. physikal. Chem.*, 1895, **16**, 477). The agreement between the various values is satisfactory, the largest deviation being for hexoic and propionic acid, where our value of K_r is 6% higher than Dippy's value and nearly 2% higher than Franke's.

The figure shows log K_r plotted against $1/T$; the inversions in strength are clearly demonstrated and the inversion temperatures are given in the table. Furthermore, both *n*-valeric and *n*-hexoic acid change

Logarithm of relative dissociation constant versus temperature.



Curve 1, *Butyric–propionic* (*Harned*); 2, n-*valeric–propionic* (*open circles*); 3, n-*hexoic–propionic* (*black circles*); 4, iso*butyric–propionic*; 5, iso*valeric–acetic*; 6, *butyric–acetic* (*Harned*).

their strength relative to *iso*butyric acid at about 26°. Harned's experimental data for the acid pairs butyric–propionic and butyric–acetic are also included in the figure. The lines obtained are straight within the limits of experimental error over the temperature range examined; their slope gives ΔH_r, the difference $(\Delta H_2 - \Delta H_1)$ between the heats of ionisation of the two acids at the same temperatures, *i.e.*, the heat change accompanying the reaction $HA_2 + A_1 \longrightarrow HA_1 + A_2$. Experiments over a wider range would be required to determine to what extent ΔH_r varies with temperature.

Approximate values (± 2°) of the temperature T_m at which log K (for acid 2) is a maximum were calculated knowing T_m for acetic and propionic acid and assuming ΔC_p for the ionisation process to be − 35 cals./deg.-mole for all the acids considered.

Discussion.

The data now presented show conclusively that inversions in the strength of the fatty acids do occur within the experimental range, and that other inversions may be expected in cases where dissociation constants differ by up to about 10% at room temperature.

A full discussion must await further more detailed work on the thermodynamics of these equilibria. Meanwhile we wish to make two points. (1) Our data indicate that for all the acids examined the temperatures (T_m) of maximum log K are well below room temperature. The low value (+ 8°) shown by *n*-butyric acid, compared with 20—25° for the earlier members of the series, was regarded as a sign of the anomalous behaviour of this acid and was attributed by Dippy to hydrogen bonding between the terminal hydrogen atoms of the hydrocarbon chain and the carboxylate ion. This behaviour was also predicted for higher acids in the *n*-series. The fact that the low values of T_m are also shown by *iso*butyric and trimethylacetic acids, in which this effect is not expected, suggests that some other interpretation is to be sought. (2) If rotation is strongly resisted in the butyrate ion we should expect this to be reflected in

anomalous values for the entropy and heat capacity changes accompanying ionisation; there seems to be little evidence of such behaviour.

This work was carried out during the tenure by one of us (D. H. E.) of an I.C.I. Fellowship, and by the other of a D.S.I.R. Maintenance Grant. We are indebted to Mr. J. H. Wolfenden for access to Tully's and Levi's results before publication.

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205. *Steroids and the Walden Inversion. Part III.* (a) *Derivatives of 6-Ketocholestane;* (b) *A Direct Proof of the Stereochemical Orientation of the Hydroxyl Group in Cholesterol.*

By C. W. SHOPPEE.

On the assumption that the hydroxyl group in cholesterol and dihydrocholesterol is (β)-orientated (*i.e.*, projects above the general plane of the steroid nuclear ring system, as also do the angular methyl groups), the configurations of various C_3-substituted derivatives of cholestane (Part I; *J.*, 1946, 1138) and cholest-5-ene (Part II; *J.*, 1946, 1147) have been established. In Section (*a*) these results are applied to establish the configurations at C_3 of analogous derivatives of 6-ketocholestane and related compounds.

In Section (*b*), a direct proof of the (β)-orientation of the hydroxyl group in cholesterol is given; all configurations at C_3 assigned in Parts I and II, and in Section (*a*), thus become established independently of the previous assumption and are subject to qualification only in so far as future determination of the absolute configuration of some steroid centre of asymmetry may prove the actual stereochemical arrangement of the steroid nucleus to be the mirror-image of that at present accepted by convention.

IN Part I (*J.*, 1946, 1138), the configurations of the epimeric 3-chlorocholestanes were established by reference to the assumed structure of dihydrocholesterol as 3(β)-hydroxycholestane, and in Part II (*J.*, 1946, 1147) the configuration of cholesteryl chloride as 3(β)-chlorocholest-5-ene was derived from its relationship to 3(β)-chlorocholestane. The consistent collation of a large body of data so achieved thus depends on the truth of the basic assumption that the hydroxyl group in cholesterol and dihydrocholesterol is (β)-orientated. In Section (*a*) consideration on the same basis is now extended to the stereochemical orientation at C_3 of derivatives of 6-ketocholestane and certain closely related compounds; in Section (*b*) a direct proof of the (β)-configuration of the hydroxyl group in cholesterol is given.

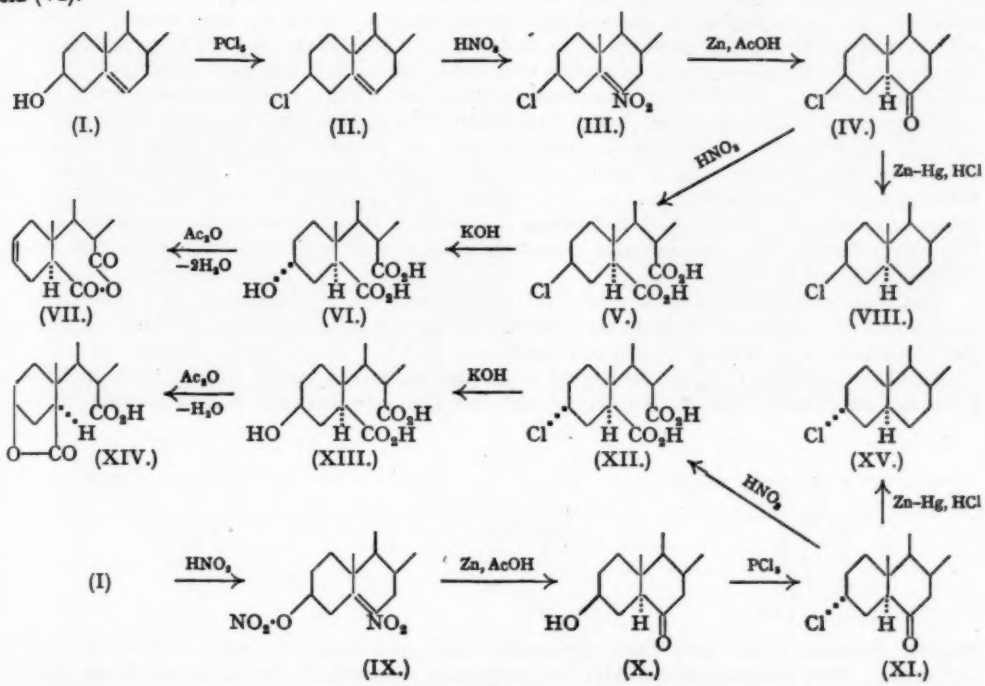
(a) *Derivatives of 6-Ketocholestane.*

In Part I (*loc. cit.*) it was shown that cholesterol (I) undergoes substitution with preservation of configuration to give cholesteryl chloride which is 3(β)-chlorocholest-5-ene (II). Nitration of (II) and reduction of the resulting 3(β)-chloro-6-nitrocholest-5-ene (III) (Mauthner and Suida, *Monatsh.*, 1903, **24**, 648; Windaus and Dalmer, *Ber.*, 1919, **52**, 162) gives the so-called "α"-chlorocholestan-6-one, m. p. 131°, which is therefore 3(β)-chlorocholestan-6-one (IV) * (cf. Ladenburg, Chakravorty, and Wallis, *J. Amer. Chem. Soc.*, 1939, **61**, 3483; Blunschy, Hardegger, and Simon, *Helv. Chim. Acta*, 1946, **29**, 199). The (β)-configuration so assigned is confirmed by Clemmensen reduction of (IV) to 3(β)-chlorocholestane (VIII) (Vanghelovici and Angelescu, *Bul. Soc. Chim. România*, 1935, **17**, 177), whilst membership of the cholestane series is proved by conversion into cholestan-6-one (Windaus and von Staden, *Ber.*, 1921, **54**, 1059) which by Clemmensen reduction gives cholestane (Windaus and Dalmer, *loc. cit.*). Windaus and von Staden (*loc. cit.*) by oxidation of (IV) with nitric acid obtained an "α"-chlorodicarboxylic acid, m. p. 263°, which can now be described as 3(β)-chlorocholestane-6‖7-dicarboxylic acid (V). Windaus and von Staden (*loc. cit.*) found the acid (V) to be unaffected by treatment with 0·5N-potassium hydroxide at 50°, but to undergo hydrolysis with 4·5N-potassium hydroxide at 100° to give an "α"-hydroxydicarboxylic acid, m. p. 218°. We shall assume provisionally that hydrolysis is here accomplished by a simple bimolecular substitution

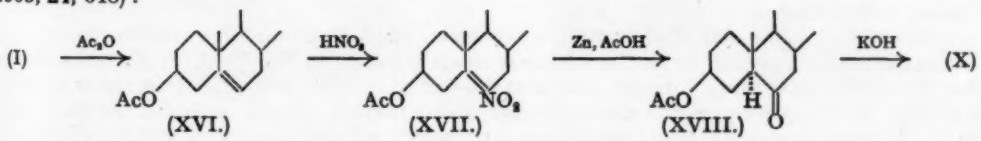
* The bromocholestanone, m. p. 123° (Windaus, *Ber.*, 1904, **37**, 2027; Blunschy, Hardegger, and Simon, *loc. cit.*), is similarly 3(β)-bromocholestan-6-one.

The ketone, m. p. 97°, obtained by Vanghelovici and Angelescu (*loc. cit.*) by treatment of 3(β)-chlorocholestan-6-one (IV) with sodium amalgam in boiling ethanol, described as "*iso*cholestan-6-one," but suggested to be the as yet unknown coprostan-6-one, is *i*-cholestan-6-one, m. p. 97° (Heilbron, Hodges, and Spring, *J.*, 1938, 759) and not cholestane-6-one, m. p. 98—99° (Windaus, *Ber.*, 1920, **53**, 488).

(mechanism S_N2) and so results in substantially complete inversion of configuration (see below); on this basis the hydroxy-acid is to be regarded as 3(α)-hydroxycholestane-6‖7-dicarboxylic acid (VI).



When cholesterol (I) is treated with nitric acid at − 15° (cf. Heilbron, Jackson, Jones, and Spring, *J.*, 1938, 104) it is converted into 6-nitrocholesteryl nitrate (IX) which by treatment with zinc and acetic acid and subsequent hydrolysis gives cholestan-3(β)-ol-6-one (X) (Windaus, *Ber.*, 1903, **36**, 3752; cf. Windaus and von Staden, *Ber.*, 1921, **54**, 1059). The incidental esterification of the hydroxyl group in the nitration of cholesterol and subsequent removal of the nitro-group by hydrogenolysis or hydrolysis cannot affect the orientation of the oxygen atom attached to C_3. Moreover, a conversion of (I) into (X), during which the hydroxyl group is preserved intact, can also be effected; cholesterol (I) as cholesteryl acetate (XVI) by nitration in the presence of sodium nitrite gives 6-nitrocholesteryl acetate (XVII), which by reduction yields 3(β)-acetoxycholestan-6-one (XVIII), hydrolysed to (X) (Mauthner and Suida, *Monatsh.*, 1903, **24**, 648):



That the hydroxyl group in (X) is actually (β)-orientated is proved by Wolff–Kishner reduction to cholestan-3(β)-ol in almost quantitative yield. Membership of the cholestane series is proved by oxidation of (X) with chromium trioxide to cholestane-3 : 6-dione (Windaus, *Ber.*, 1903, **36**, 3752) reducible to cholestane (Windaus, *Ber.*, 1917, **50**, 133).

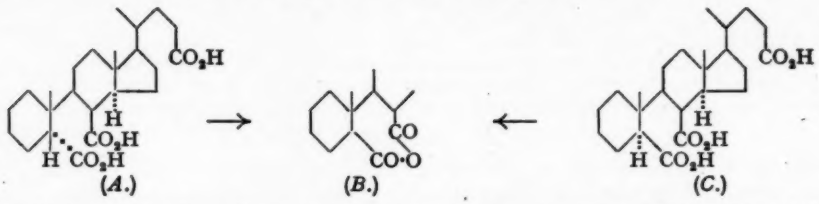
In Part I (*loc. cit.*) it was shown that in saturated derivatives of cholestane replacement of a hydroxyl group at C_3 by chlorine using phosphorus pentachloride leads to inversion of configuration; if, owing to the heavy damping imposed by passage through two saturated carbon atoms, the polar effect at C_3 of the carbonyl group at C_6 in (X) may be regarded as very small, then treatment of (X) with one molecule * of phosphorus pentachloride should lead to

* The enolic form of (X) does not appear to be involved; for although this as the entity undergoing substitution would lead to retention of configuration at C_3 because of the influence of the $C_5:C_6$-double bond, then up to 50% yield of the as yet unknown 3(β) : 6-dichlorocholest-5-ene should appear in the reaction product.

substitution with practically complete inversion of configuration. The so-called " β "-chlorocholestan-6-one, m. p. 181°, so prepared (Windaus and Stein, *Ber.*, 1904, **37**, 3699; Windaus and von Staden, *loc. cit.*) is accordingly 3(α)-chlorocholestan-6-one (XI); structurally, it differs from (IV) only in respect of the configuration of the chlorine atom at C_3, since both (IV) and (XI) by treatment with boiling quinoline give cholest-2-en-6-one (Blunschy, Hardegger, and Simon, *loc. cit.*), whilst Windaus and von Staden also state (*Ber.*, 1921, **54**, 1060) that both (IV) and (XI) yield cholestan-6-one by treatment unspecified. Finally, Clemmensen reduction of (XI) gives 3(α)-chlorocholestane (XV). Oxidation of (XI) with nitric acid (Windaus and Stein, *loc. cit.*) furnishes a " β "-chlorodicarboxylic acid, m. p. 243°, which is clearly 3(α)-chlorocholestane-6‖7-dicarboxylic acid (XII); this acid is readily hydrolysed by brief treatment with 0·5N-potassium hydroxide at 50° to a " β "-hydroxydicarboxylic acid, m. p. 242°. We shall again provisionally assume that hydrolysis occurs by a simple bimolecular substitution (S_N2) and so proceeds with substantially complete inversion to give 3(β)-hydroxycholestane-6‖7-dicarboxylic acid (XIII).

The two hydroxy-acids (VI) and (XIII) differ only in configuration at C_3, because by oxidation with chromium trioxide they afford the same 3-ketocholestane-6‖7-dicarboxylic acid (Windaus and Stein, Windaus and von Staden, *locc. cit.*).

The hydroxy-acid (VI) by treatment with hot acetic anhydride and vacuum distillation gives the unsaturated anhydride (VII); * this is a neutral substance, non-extractable from its



(*A.*) (*B.*) (*C.*)

ethereal solution with 2N-sodium carbonate, and non-titratable with cold 0·01N-sodium hydroxide. The hydroxy-acid (XIII) was originally reported by Windaus and Stein (*loc. cit.*, p. 3705) to pass by extended treatment with hot acetyl chloride into an anhydro-compound, m. p. 212—214°, which these authors state " wohl sicher als Anhydrid und nicht als Lactonsäure anzusehen ist ", because it appeared in that part of the reaction product which was insoluble in sodium carbonate. The subsequent investigation of Lettré (*Ber.*, 1935, **68**, 766), now confirmed, shows that the acid (XIII) by brief treatment with hot acetic anhydride readily gives an anhydro-compound, m. p. 214°, which is the lactonic acid (XIV); it is now found that this cannot be extracted from its ethereal solution with sodium carbonate, titrates as a monobasic acid with cold 0·01N-sodium hydroxide, and reacts with diazomethane to give the lactonic *methyl* ester. The formation of a lactonic acid from the acid (XIII) only is consistent with its formulation as a 3(β)-hydroxy-acid in which both the hydroxyl group at C_3 and the carboxyl group attached to C_5 lie on the same side of, and by convention above, the general plane of the original nuclear ring *A*.

Examination of models mechanically so constructed as to permit free rotation about the bond-axes (for the loan of which the author is much indebted to Mr. W. A. Wightman) shows that if the *cyclo*hexane ring, formerly ring *A* of the steroid nucleus, is a chair-form, then, because the chair is completely rigid, the hydroxyl and carboxyl groups, situated as they are on non-adjacent carbon atoms, cannot interact to yield a γ-lactone with C–C and C–O bonds of normal length (cf. Fig. 1). If, however, the *cyclo*hexane ring is a boat-form, which is highly mobile, an arrangement can readily be achieved which appears to render normal γ-lactone formation not only possible but almost inevitable (cf. Fig. 2). Since it has been shown that the chair ⟶ boat transformation in *cyclo*hexane is a relatively facile process (Part I), such a transformation may, indeed must, be regarded as preceding lactone formation. It remains to be added that the models confirm that an (α)-orientated hydroxyl group at C_3 cannot interact

* The statement that 3(α)-hydroxycholestane-6‖7-dicarboxylic acid (VI) does not form a lactone (Sobotka, " The Chemistry of the Sterids ", Baltimore, 1938, p. 61; Strain, Gilman's " Organic Chemistry ", New York, 1943, Vol. II, p. 1376) appears to be without experimental foundation apart from the evidence now given in this paper. The non-formation of a pyro-ketone here may be compared with the case of cholane-6‖7 : 24-tricarboxylic acid (thilobilianic acid) (*A*) (Wieland and Dane, *Z. physiol. Chem.*, 1932, **210**, 268) and 5-*allo*cholane 6‖7 : 24-tricarboxylic acid (*allo*thilobilianic acid) (*C*) (*idem*, *ibid.*, 1932, **212**, 41) which by pyrolysis at 290° yield the same anhydride (*B*), with inversion at C_5 in one case, and not the expected pyro-ketone.

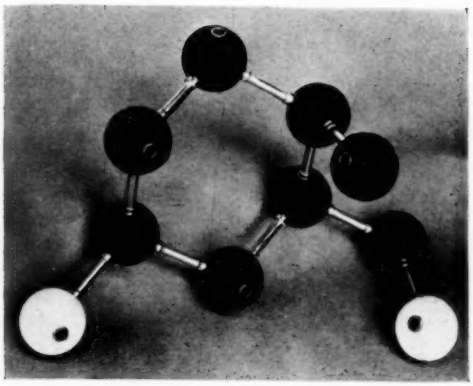


FIG. 1.
The acid (XIII) *as a chair-form.*

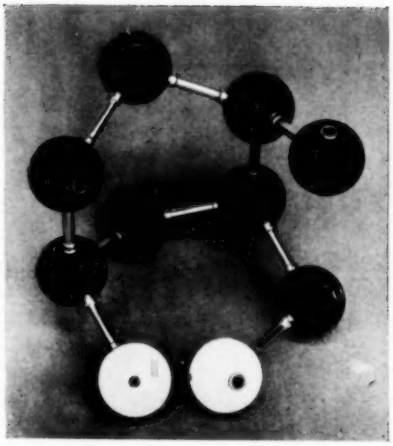


FIG. 2.
The acid (XIII) *as a boat-form.*

(The white spheres represent the oxygen atoms of the hydroxyl group at C_3 *and the hydroxyl group of the carboxyl group attached to* C_5*.)*

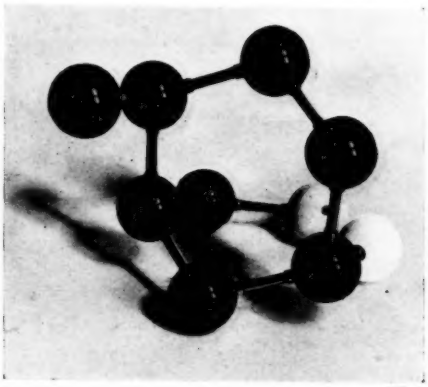


FIG. 3.
The acid (XX) *as a chair-form.*

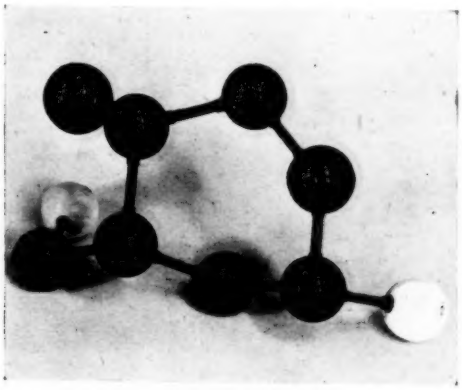


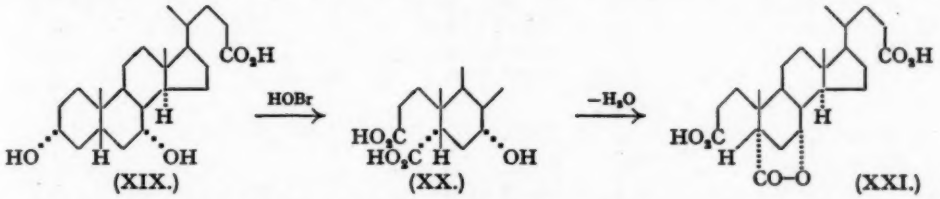
FIG. 4.
The acid (XX) *as a boat-form.*

(The white spheres represent the oxygen atoms of the hydroxyl group at C_3 *and the hydroxyl group of the carboxyl group attached to* C_7*.)*

[*To face p.* 1034

with a (β)-orientated carboxyl group attached to C_8, as in the 3(α)-hydroxy-acid (VI), either in the chair- or the boat-form, to give a γ-lactone.

The ready conversion of the 7(α)-hydroxytricarboxylic acid (XX), derived from chenodeoxycholic acid (XIX) by oxidation with hypobromite, into the lactonic acid (XXI) (Windaus and v. Schoor, *Z. physiol. Chem.*, 1926, **157**, 181; cf. Borsche and Franck, *Ber.*, 1926,



(XIX.) (XX.) (XXI.)

59, 1748) represents an analogous but stereochemically inverse case. Both the hydroxyl group at C_7 and the carboxyl group attached to C_8 are (μ)-orientated, *i.e.*, they lie on the same side of, and by convention below, the general plane of the original nuclear ring *B*; if the *cyclo*hexane ring bearing them is a chair-form (cf. Bastiansen and Hassell, *Nature*, 1946, **157**, 765) then production of a γ-lactone with bonds of normal lengths appears to be a natural consequence (cf. Fig. 3). If the *cyclo*hexane ring is, however, a boat-form [cf. the structure for coprostane proposed by Ruzicka, Furter, and Thomann (*Helv. Chim. Acta*, 1933, **16**, 331)], then owing to incorporation in another rigid ring system (ring *C must* be a chair-form), γ-lactone formation appears to be impossible (cf. Fig. 4).

The reaction sequence (I $\xrightarrow{IX}$ XIV) has previously been considered by Lettré (*loc. cit.*) on the assumption that cholesterol is a 3(β)-hydroxy-compound, but without the knowledge, provided by this series of papers, of the configuration of the intermediates. Conversely, other authors (Miescher and Fischer,* *Helv. Chim. Acta*, 1938, **21**, 336, especially 352; Sobotka, " The Chemistry of the Sterids ", pp. 60, 61; Bergmann,† *Chem. and Ind.*, 1939, **58**, 512) have attempted to derive from the (β)-configuration of the hydroxyl group in (XIII), but in the absence of knowledge of the stereochemical orientation at C_3 of the various intermediates in the transformation of (I) into (V) and (I) into (XII), a proof of the proposal made by Ruzicka (Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 327; Ruzicka, Brüngger, Meyer, and Eichenberger, *ibid.*, 1934, **17**, 1407) on the basis of the Auwers–Skita rule that the hydroxyl group in cholesterol is (β)-orientated. As Ruzicka himself has pointed out (Ruzicka, Goldberg, Meyer, Brüngger, and Eichenberger, *ibid.*, p. 1395; Ruzicka, Goldberg, and Wirz, *ibid.*, 1935, **18**, 61) use of the Auwers–Skita rule involves an element of uncertainty; ‡ moreover, there is a further element of uncertainty in regard to the stereochemical course of the replacement of chlorine by hydroxyl in the hydrolysis of the chloro-acids (V) and (XII). If both these reactions proceeded with preservation of configuration the conclusion would be that the hydroxyl group in cholesterol is (α)-orientated; or, conversely, that all the transformations discussed above, and in Parts I and II, should and could consistently be re-formulated on the basis that cholesterol is an (α)-hydroxy-compound. On this account it is necessary here more closely to examine the validity or otherwise of the provisional assumption, made above, that alkaline hydrolysis of the epimeric chloro-acids (V) and (XII) proceeds by a simple bimolecular mechanism (S_N2) with substantially complete inversion of configuration.

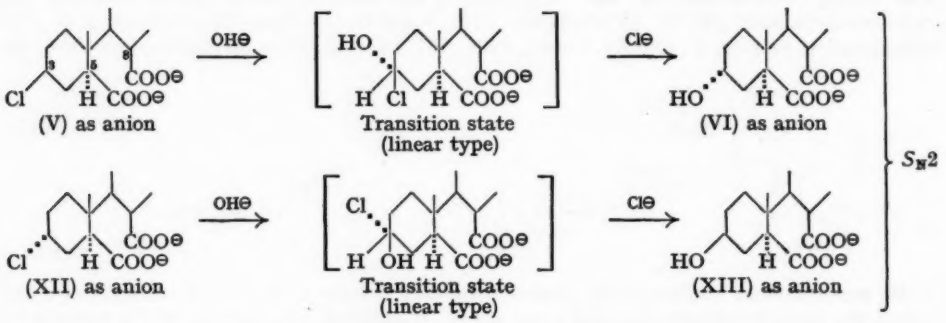
The system involved in these reactions is analogous to that present in 3-chlorobutane-1-carboxylic acid. Alkaline hydrolysis of (±)-3-bromobutane-1-carboxylic acid at 15° leads

* Miescher and Fischer say: " Dass zweimalige *Walden*'sche Umkehrung durch Ersatz von Hydroxyl in (X) durch Chlor und durch Rückwandlung von Chlor in (XII) in Hydroxyl eintritt, und damit die sterische Lage der Hydroxylgruppe erhalten bleibt, wird durch neuere Befunde in der Sterinreihe von Ruzicka (*Helv. Chim. Acta*, 1935, **18**, 998; 1936, **19**, 1407) und Marker (*J. Amer. Chem. Soc.*, 1935, **57**, 2358; 1936, **58**, 481) *erwiesen* ". This is incorrect, for none of these papers *proves* the stereochemical configuration at C_3 of the compounds in question; use of the verb *erwiesen* is unwarranted, and it may be remarked that Miescher and Fischer conclude the paragraph containing the above quotation by the words " so wäre doch noch eine Ergänzung des Beweismaterials erwünscht ".

† Contrary to the statement of Bergmann, the *absolute* configuration of any centre of asymmetry in the steroid nucleus has not yet been determined.

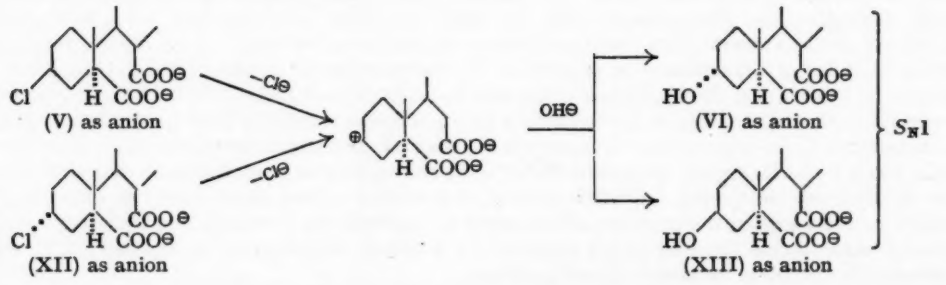
‡ The Auwers–Skita rule states that catalytic hydrogenation of a carbonyl group in an acidic medium usually gives *cis*-forms, but in a neutral medium leads to *trans*-forms. It is uncertain whether the C_3–H bond or the C_3–C_4 bond should be considered in applying the rule, and choice of the latter alternative would lead to configurations at C_3 opposite to those conventionally attributed to dihydrocholesterol, coprostanol, and their epimerides.

directly to γ-valerolactone (Fittig and Messerschmidt, *Annalen*, 1881, **208**, 94; Fittig and Frānkel, *ibid.*, 1889, **255**, 30), but, were data available as to the steric course of hydrolysis for the



(+)- and (−)-enantiomorphs, it seems improbable that they could contribute to the elucidation of our case involving the acids (V) and (XII), in which inclusion of the system in a six-membered ring limits the relative spatial positions of the chlorine atom at C_3 and the carboxylate-ion group attached to C_5. Since polar effects are known to suffer heavy damping by transmission through saturated carbon atoms, the effect so propagated of the carboxylate-ion group attached to C_5 (and likewise, *a fortiori*, of the carboxylate-ion group at C_8) on the steric course of substitution at C_3 should be small. The electrostatic field of the carboxylate-ion groups may well increase the activation energy of the transition state by several kg.-cals./mole by virtue of the extra work required for the approach of the attacking hydroxyl ion; nevertheless, it seems probable in view of the influence of the geometrical character of the steroid nucleus upon the form of the transition state that the substitution of Cl by OH in (V) and (XII) occurs by mechanism S_N2 with substantially complete inversion to give respectively the anions of the acids (VI) and (XIII).

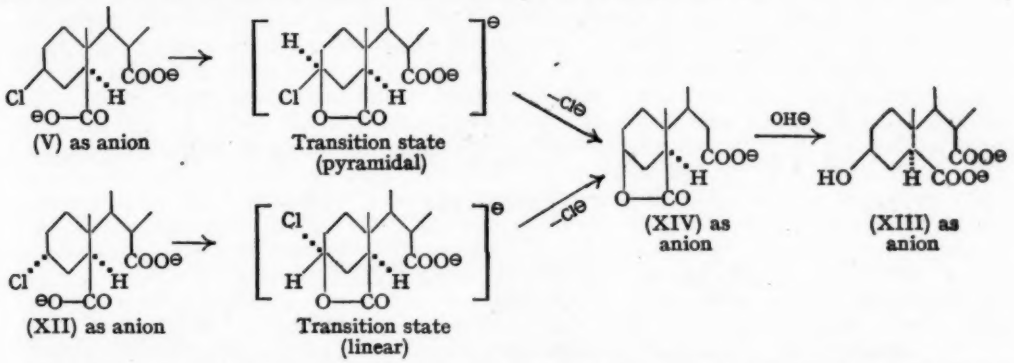
An alternative possibility, however, is that hydrolysis of the chloro-acids (V) and (XII) proceeds by mechanism S_N1, although it seems improbable that the electron-repulsion of the carboxylate-ion groups, transmitted through the chain of saturated carbon atoms, could afford effective facilitation of such a process.



If the carboxylate-ion group attached to C_5 does not intervene to influence the steric course of the reaction undergone by the intermediate ion, then the stereochemical result must be local but very nearly complete racemisation with production of very nearly equal quantities of the 3-epimeric hydroxy-acids (VI) and (XIII). If the carboxylate-ion group attached to C_5 does intervene to preserve configuration at C_3, then, as a consequence of the electrostatically maintained pyramidal configuration of the intermediate ion, the common product must be (VI) and not (XIII). It was found by Windaus *et al.* (*locc. cit.*), and is now confirmed, that hydrolysis of the chloro-acids (V) and (XII) furnishes high yields of individual epimeric hydroxy-acids; we therefore conclude that hydrolysis does not occur by mechanism S_N1. This conclusion is substantiated by the circumstance that hydrolysis is brought about in the presence of considerable concentrations of hydroxyl ions, and it is known that mechanism S_N2 increases in importance, relative to a possible competitive mechanism S_N1 facilitated by electron-repelling substituents, as the hydroxyl-ion concentration increases (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 187).

The polar effect of the carboxylate-ion group attached to C_5 might, however, become effective

in another way, the carbon atom (C_3), bearing the chlorine atom, being attacked directly to give rise to an intramolecular modification of the bimolecular mechanism.



In this case, the molecular geometry of the chloro-acid (V) determines the form of the transition state and would lead inevitably to the pyramidal type, which corresponds with retention of configuration and would furnish the anion of the lactonic acid (XIV), which by subsequent acyl–oxygen fission (corresponding to ordinary alkaline ester hydrolysis), which cannot cause inversion, would give the hydroxy-acid (XIII).

It may be noted that the formation of such a pyramidal transition state is rendered intrinsically unlikely because the exclusion principle shows the required energy of activation will be prohibitively high; further, the electrostatic factor arising from the mutual repulsion of the dipole field in the C–Cl link and the anionic charge of the carboxylate-ion group must also impede the formation of a pyramidal transition state, $C\begin{matrix}\cdots O^{-}(\delta-)\\ \cdots Cl\ (\delta-)\end{matrix}$. Application of an analogous intramolecular mechanism to the chloro-acid (XII) would produce the anion of the *same* lactonic acid (XIV), because here the molecular geometry of the chloro-acid (XII) again determines the form of the transition state but leads inevitably to the linear type, the consequence of which is inversion of configuration. Since it is established experimentally that hydrolysis of the chloro-acids (V) and (XII) furnishes high yields of individual epimeric hydroxy-acids, the foregoing intramolecular mechanism is excluded.

We conclude therefore that it is highly probable that the conversion of the chloro-acids (V) and (XII) proceeds by mechanism S_N2 with substantially complete inversion of configuration, and, with Miescher and Fischer, Sobotka, and Bergmann, that the hydroxyl-group in cholesterol is (β)-orientated.

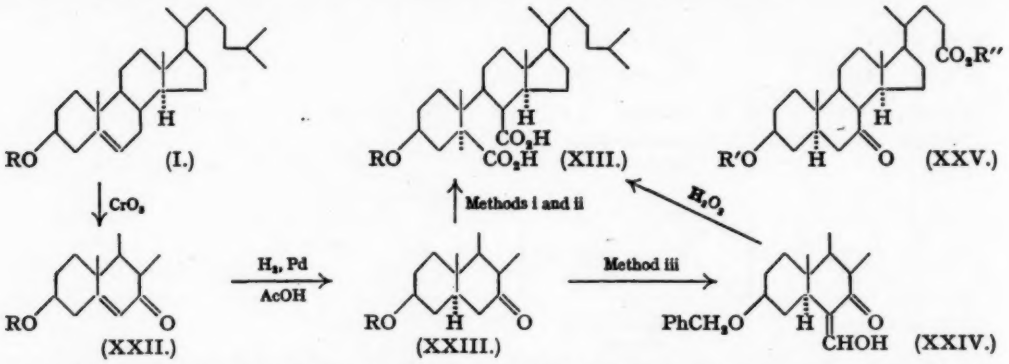
(b) *A Direct Proof of the Stereochemical Orientation of the Hydroxyl Group in Cholesterol.*

The foregoing analysis shows that it is highly probable that the (β)-configuration of the hydroxyl group of the hydroxy-acid (XIII) can justifiably be related to the configuration of the hydroxyl group in cholesterol (I) in the light of knowledge now adduced as to the configuration at C_3 of the various intermediates. There remains, however, an element of uncertainty in regard to the steric course of the conversion of the chloro-acids (V) and (XII) into the hydroxy-acids (VI) and (XIII). In view of the importance of the matter and this defect in the argument, it seemed desirable to evolve a flawless proof of the stereochemical orientation of the hydroxyl group in cholesterol.

In order to give such a proof, it is necessary to preserve intact the vital hydroxyl group during conversion of cholesterol (I; R = H) into the hydroxy-acid (XIII; R = H), and three methods, involving protection of the hydroxyl group by suitable acylation or alkylation, were envisaged. All three methods possess common initial stages: (*a*) the well-established oxidation of cholesterol esters (I) to the 7-ketocholesteryl compounds (XXII), (*b*) hydrogenation of the latter to the corresponding derivatives of 7-ketocholestane (XXIII).

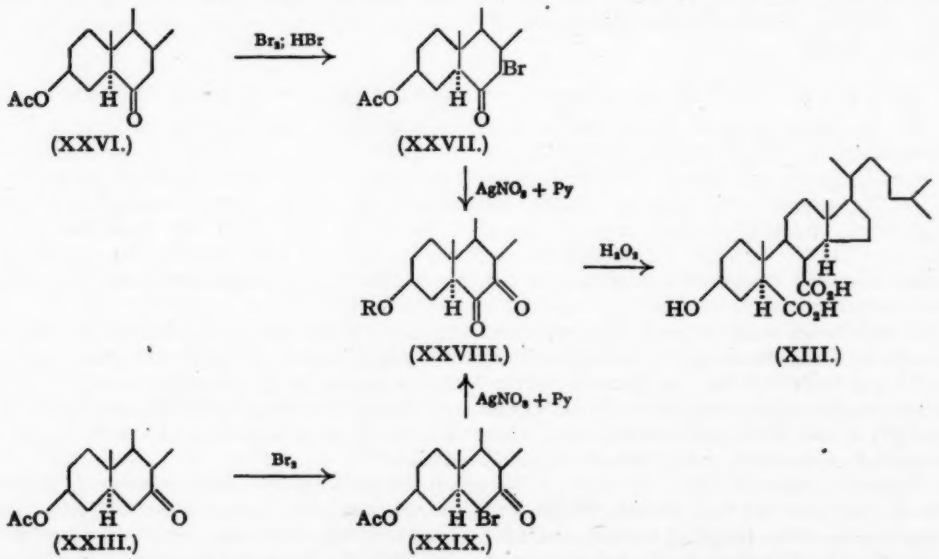
Method (i) (with Dr. W. C. J. Ross). The direct oxidation with chromium trioxide in acetic acid of 7-ketocholestanyl acetate (XXIII; R = Ac) and chromatographic analysis of the methyl esters of the resulting acetoxy-acids led to the isolation as the sole crystalline product of *methyl 7-keto-3(β)-acetoxy-5-allocholanate*, m. p. 133° (XXV; R′ = Ac, R″ = Me), hydrolysed to *3(β)-hydroxy-7-keto-5-allocholanic acid*, m. p. 193° (XXV; R′ = R″ = H). The subsequent discovery that methyl 3(β)-acetoxycholestane-6‖7-dicarboxylate (dimethyl ester of XIII;

R = Ac) is non-crystalline led later to the alkaline hydrolysis of the individual non-crystallisable fractions, but from none of these could the acid (XIII; R = H) be isolated.



Method (ii) (with Dr. N. GOUGH). This involved the oxidation of 7-ketocholestanyl benzoate (XXIII; R = Bz) with potassium hypoiodite (cf. Wettstein, Fritzsche, Hunziger, and Miescher, *Helv. Chim. Acta*, 1941, **24**, 332E; Heer and Miescher, *ibid.*, 1945, **28**, 156); it was hoped that the greater resistance to hydrolysis of benzoyloxy- as compared with acetoxy-groups (cf. Ruzicka, Wettstein, and Kagi, *ibid.*, 1935, **18**, 1478; Shoppee, *J.*, 1946, 1134) might permit extensive oxidative fission of ring *B* between C_6 and C_7 before hydrolysis of the protecting benzoyl group occurred. This hope proved to be unfounded, because large quantities of benzoic were readily isolated from the acidic fraction of the reaction product; the residual acidic material proved intractable and was probably a complex mixture containing cholestane-2‖3- and -3‖4-dicarboxylic acids among other products.

Method (iii). As originally envisaged, this involved conversion of 7-keto-3(β)-benzyloxycholestane (XXIII; R = CH_2Ph) by condensation with ethyl formate into the 7-keto-6-hydroxymethylene compound (XXIV), with subsequent fission of ring *B* with alkaline hydrogen peroxide to the benzyloxy-acid (XIII; R = CH_2Ph) (cf. Billeter and Miescher, *Helv. Chim. Acta*, 1946, **29**, 859) and final hydrogenolysis of the protecting benzyl group to the hydroxy-acid (XIII; R = H) (cf. Heer and Miescher, *ibid.*, 1945, **28**, 156). It was, however, discovered that a compound, even more suitable than (XXIV) and readily available, had already been described by Heilbron, Jones, and Spring (*J.*, 1937, 801); these authors obtained from 6-ketocholestanyl



acetate (XXVI) [Formula XVIII of Section (*a*)] by bromination, isomerisation of the first-formed 5-bromo-derivative to 7-bromo-6-ketocholestanyl acetate (XXVII) and oxidation of this

with silver nitrate in pyridine, the acetoxy-diketone (XXVIII; R = Ac). And in fact an oxidation with hydrogen peroxide of the hydroxy-diketone (XXVIII; R = H) was actually carried out by Dr. E. R. H. Jones in 1937 (private communication, see below) with a view to establishing the positions at C_6 and C_7 of the two carbonyl groups in (XXVIII). The acid resulting from this oxidation could not be satisfactorily identified; it melted at 225—226°, and although it failed to depress the m. p. (239—240°) of a genuine specimen of the hydroxy-acid (XIII), it gave unsatisfactory results on analysis (Found: § C, 70·0, 70·4; H, 9·6, 9·5. Calc. for $C_{27}H_{46}O_5$: C, 71·96; H, 10·29%). The matter was not further pursued because in 1938 the structure of the acetoxy-diketone (XXVIII; R = Ac) was secured by its preparation from 7-ketocholestanyl acetate by Barr, Heilbron, Jones, and Spring (*J.*, 1938, 334). This preparation has been repeated; 7-ketocholestanyl acetate (XXIII) was converted into the 6" β "-bromo-derivative, m. p. 143° (XXIX), which by oxidation with silver nitrate in hot pyridine readily gave the acetoxy-diketone (XXVIII; R = Ac), which was also obtained from a specimen of the 7-bromo-6-keto-compound (XXVII) kindly supplied by Dr. Jones. The acetoxy-diketone (XXVIII; R = Ac) was hydrolysed with dilute methanolic potassium hydroxide at 20° to the *hydroxy-diketone* (XXVIII; R = H), which gave a green colour with alcoholic ferric chloride solution, and this was oxidised with alkaline hydrogen peroxide.

Windaus and Stein (*Ber.*, 1904, **37**, 3705) observed that the hydroxy-acid (XIII) retained 1 mol. of water after drying in a vacuum (Found: * C, 69·61; H, 10·55. Calc.† for $C_{27}H_{46}O_5,H_2O$: C, 69·19; H, 10·32%), but obtained excellent figures after drying at 110° for an unspecified period and at an unspecified pressure (Found: * C, 72·01; H, 10·41. Calc.† for $C_{27}H_{46}O_5$: C, 71·96; H, 10·29%). Since it is known that steroids with free hydroxyl groups may retain water with great tenacity, it appeared possible that the low m. p. and unsatisfactory analyses obtained by Dr. Jones and recorded above might be due to this cause. The crystalline acid resulting from the oxidation of the hydroxydiketone (XXVIII; R = H) was dissolved in a little anhydrous dioxan and dried by repeated azeotropic distillation with benzene; the acid, so obtained, crystallised from acetone–pentane in aggregates of felted needles, m. p. 241—242°, either alone or admixed with a genuine specimen of 3(β)-hydroxycholestane-6‖7-dicarboxylic acid (XIII); this was prepared by the method of Windaus and Stein (*Ber.*, 1904, **37**, 3704), subjected to thorough drying as described above, and crystallised from acetone–pentane to give aggregates of felted needles, m. p. 241—242°. The acid obtained by Dr. Jones in 1937, and kindly made available by him, was originally crystallised repeatedly (following Windaus and Stein, *loc. cit.*) from aqueous acetone. It formed flat plates which became opaque at 130—140°, and melted at 226—228°; by thorough drying as described above and crystallisation from acetone–pentane, there were obtained characteristic aggregates of felted needles, m. p. 241—242°, alone or on admixture with the other specimens of the same m. p. For further identification the specimens of the hydroxy-acid (XIII) obtained by the foregoing degradation and by the method of Windaus and Stein (*loc. cit.*) were converted by brief treatment with boiling acetic anhydride into the lactonic acid (XIV) (Lettré, *loc. cit.*); both preparations had m. p. 214—215° and gave no depression on admixture. The dimethyl ester and acetoxy-dimethyl ester of the two specimens of the acid (XIII) were prepared for further comparison, but could not be induced to crystallise.

The absolute configuration of no single steroid centre of asymmetry has yet been determined, and it may be that the actual stereochemical arrangement of the cholesterol molecule will prove to be the mirror-image of that accepted by convention today. Subject only to this reservation, it can now be stated that the hydroxyl group situated at C_3 in cholesterol is (β)-orientated.

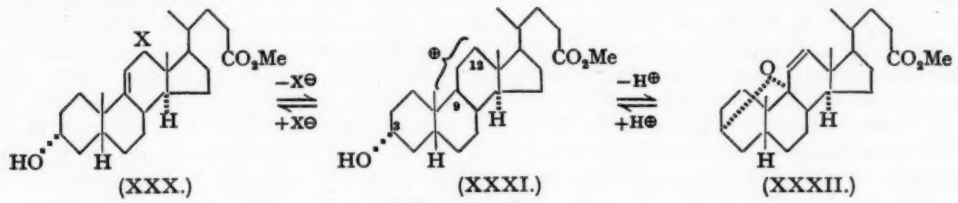
A similar statement can be made in respect of " β "-sitosterol, stigmasterol, and ergosterol since these substances have been converted into 3(β)-acetoxynor*allo*cholanic acid (Wieland, Dane, and Martius, *Z. physiol. Chem.*, 1933, **215**, 15; Fernholz and Chakravorty, *Ber.*, 1934, **67**, 2021), and in respect of *all* 3-hydroxy-steroids which, directly or indirectly, have been correlated with cholesterol in regard to configuration at C_3, *e.g.*, the cortical substances A, D, J, K, L, N, O, P, R, and V (Reichstein and Shoppee, " Vitamins and Hormones ", 1943, I, 345), the cardiac aglycones digitoxigenin (Hunziker and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 1472), gitoxigenin (K. Meyer, *ibid.*, 1946, **29**, 718, 1580), and scillarene-A (Stoll and Renz, *ibid.*, 1941, **24**, 1380), and the steroid sapogenins, sarsasapogenin, smilagenin, tigogenin, *neo*tigogenin, chlorogenin, and diosgenin (Shoppee, *Ann. Rev. Biochem.*, 1942, XI, 103).

Since this work was commenced, an indirect proof of the (β)-orientation of the hydroxyl

* Windaus and Stein's analytical figures have been recalculated using modern atomic weights.

† Windaus and Stein based their calculated figures on the cholesterol formula, $C_{27}H_{44}O$, in use in 1904, and so give the molecular formula of the hydroxy-acid (XIII) as $C_{27}H_{44}O_5$.

group in cholesterol has been given by Kendall *et al.* (*J. Biol. Chem.*, 1946, **164**, 569). These workers show that deoxycholic acid can be converted into methyl 12-halogeno-3(α)-hydroxychol-9(11)-enate (XXX); this is stable in anhydrous non-polar solvents, but by treatment in chloroform solution with water at 20° is converted almost quantitatively *via* the mesomeric ion (XXXI) into the Δ^{11}-3 : 9-oxide (XXXII), which with hydrochloric or hydrobromic acid regenerates (XXX).



X = Cl or Br

Since ether-formation does not involve inversion of configuration (Kenyon and McNicol, *J.*, 1935, **123**, 14; Hughes, Ingold, and Masterman, *J.*, 1937, 1197), and since the formation of an oxide bridge between C_3 and C_9 in the presence of the (β)-orientated angular methyl group at C_{10} can *only* occur if the oxide is a 3(α) : 9(α)-oxide, as is demonstrable by use of models,* the hydroxyl group in (XXX) and hence in deoxycholic acid must be (α)-orientated. Because the configuration of the hydroxyl group at C_3 in the bile acids is known to be the opposite of that in cholesterol, it follows by exclusion that the hydroxyl group in cholesterol is (β)-orientated.

Experimental.

All m. p.s were determined thermo-electrically on a Kofler block and are therefore corrected; limit of error ± 2°. All solvents for chromatographic analyses were specially purified and rigorously dried; for drying ethereal extracts, brief treatment with sodium sulphate was used.

Section (a).

3(β)-*Hydroxycholestane from* 3(β)-*Hydroxycholestane*-6-*one* (X).—The hydroxy-ketone (X) (m. p. 144°; 200 mg.), 100% hydrazine hydrate (0·5 c.c.), and a solution of sodium (200 mg.) in ethanol (5 c.c.) were heated at 170—175° for 6 hours. The product was poured into sufficient 2N-hydrochloric acid, the greater part of the ethanol removed under reduced pressure, and the precipitate filtered off. The dry precipitate (190 mg.) was dissolved in benzene (1 c.c.) and introduced on to a column of aluminium oxide (Spence, activity I—II, 6 g.) prepared in pentane. After elution with pentane, benzene, and ether, which removed insignificant amounts of oil, elution with acetone–ether (1 : 1) gave pure 3(β)-hydroxycholestane (161 mg.), plates from methanol, m. p. 125° with transition to needles, m. p. 141°; the same behaviour on melting was observed by admixture with a genuine specimen. Further elution of the column with acetone gave only traces of material, but use of acetone–chloroform–methanol (1 : 1 : 1) gave a little gum (20 mg.).

3(α)-*Chlorocholestane* (XV) *from* 3(α)-*Chlorocholestan*-6-*one* (XI).—3(α)-Chlorocholestan-6-one was prepared from the hydroxy-ketone (X) by treatment with phosphorus pentachloride according to Windaus and Stein (*loc. cit.*) as modified by Ruzicka *et al.* (*Helv. Chim. Acta*, 1934, **17**, 1389), and crystallised from acetic acid. The chloro-ketone (m. p. 181°; 200 mg.) was suspended in a mixture of acetic acid (2 c.c.) and concentrated hydrochloric acid (2 c.c.); amalgamated zinc wool (1 g.) was added, a slow stream of hydrogen chloride passed into the flask through a tube terminating just above the surface of the mixed acids, and the mixture heated under reflux until the original crystals became converted into semi-solid droplets. The cooled liquid was decanted from residual zinc, and excess of hydrogen chloride removed under reduced pressure; the zinc was well washed with pentane, and the pentane washings used to extract the aqueous liquid. The pentane extract was washed with water, 2N-sodium carbonate, and again with water, dried, and evaporated. The product gave a yellow colour with tetranitromethane, and to remove unsaturated by-products was treated with excess of 1% chromium trioxide solution in acetic acid on the steam-bath for 0·5 hour. After working up in the usual manner, the product was dissolved in pentane and filtered through a column of aluminium oxide (Spence, 5 g.) prepared in pentane. Evaporation of the filtrate gave an oil which crystallised by inoculation; repeated recrystallisation from acetone finally gave a poor yield of 3(α)-chlorocholestane, m. p. 100—102°, which did not depress the m. p. of a genuine specimen.

3(α)-*Hydroxycholestane*-6‖7-*dicarboxylic Acid* (VI).—This was prepared by the method of Windaus

* Mr. Wightman's models show that a 3(α) : 9(α)-oxide with normal bond lengths for the C–O–C linkage is readily formed if rings *A* and *B* of the coprostane nucleus are both boat-forms; this is not so in the case of the modification, based on a structure proposed for *cis*-decalin by Bastiansen and Hassell (*Nature*, 1946, **157**, 765), in which despite *cis*-union both rings *A* and *B* are chair-forms, but again becomes the case when ring *A* of this structure becomes a boat-form with ends at C_3 and C_{10}, and ring *B* remains a chair-form (cf. Ruzicka, Furter, and Goldberg, *Helv. Chem. Acta*, 1938, **21**, 509, Plate II, Fig. 3*a*).

Added, May 24th, 1948.—See also the discussion by Barton (this vol., p. 340).

and von Staden (*loc. cit.*); the crude acid obtained by hydrolysis of 3(β)-chlorocholestane-6||7-dicarboxylic acid (V) (m. p. 265°; 350 mg.) was dried by dissolution in a little anhydrous dioxan and repeated azeotropic distillation with benzene, and the residue (m. p. 215—220°; 293 mg.), obtained by final evaporation in a vacuum, recrystallised from dioxan to give clusters of small prisms, transformed at 200—205° into needles, m. p. 218—221°.

Cholest-2 (or ?3)-ene-6||7-dicarboxylic Anhydride (VII).—The hydroxy-acid (VI) (50 mg.) was heated with pure acetic anhydride (1 c.c.) under reflux for 0·5 hour; after removal of the reagent under reduced pressure, the residual oil was taken up in ether, and the ethereal solution washed with sodium hydrogen carbonate, 2N-sodium carbonate, and water; acidification of the alkaline washings gave no turbidity. The ethereal solution was dried, evaporated, and kept for some hours at 50° in a high vacuum (finally 0·001 mm.); the viscous oil so obtained gave no colour with tetranitromethane in chloroform solution, but could not be induced to crystallise. Analysis of the oil gave figures which suggest it to consist essentially of 3(α)-hydroxycholestane-6||7-dicarboxylic anhydride rather than the corresponding 3(α)-acetoxy-compound (Found: C, 75·47; H, 9·57. Calc. for $C_{27}H_{44}O_4$: C, 74·96; H, 10·25%. Calc. for $C_{29}H_{46}O_5$: C, 73·22; H, 9·74%). By distillation in a molecular flask at 160—180° (bath temp.)/0·001 mm., there was obtained an oil, giving a strong yellow colour with tetranitromethane in chloroform, which crystallised when moistened with methanol and kept at 0°; recrystallisation from methanol gave *cholest-2 (or ?3)-ene-6||7-dicarboxylic anhydride* as prisms, m. p. 134° (Found: C, 77·78, 77·76; H, 10·43, 10·11. $C_{27}H_{42}O_3$ requires C, 78·21; H, 10·21%). The anhydride neither discharged the colour nor evolved gas when treated with an ethereal solution of diazomethane and was recovered unchanged.

3(β)-*Hydroxycholestane-6||7-dicarboxylic Acid* (XIII).—This was prepared by the procedure of Windaus and Stein (*loc. cit.*); the crude hydroxy-acid, obtained by hydrolysis of 3(α)-chlorocholestane-6||7-dicarboxylic acid (m. p. 243°; 350 mg.), was completely dried by solution in a little anhydrous dioxan and repeated azeotropic distillation with dry benzene, and the residue (295 mg.), obtained by final evaporation in a vacuum, recrystallised from acetone–pentane, from which it separated in circular aggregates of felted needles, m. p. 241—242° (gas evolution). The *dimethyl* ester was prepared by dissolving the acid (50 mg.) in the minimum quantity of anhydrous dioxan and treating the solution with ethereal diazomethane at 0° for 0·25 hour; the yellow solution was poured into ice-cold 2N-hydrochloric acid, and the ethereal layer washed with 2N-sodium carbonate, then water, dried, and evaporated. The resulting oil could not be induced to crystallise; it was distilled in a molecular flask at 140—160° (bath temp.)/0·001 mm., but thereafter still resisted all attempts to induce crystallisation (Found: C, 72·48; H, 10·43. $C_{29}H_{50}O_5$ requires C, 72·75; H, 10·53%). The 3(β)-*acetoxy-dimethyl* ester was prepared by esterifying the acid (50 mg.) as above, and dissolving the product in pyridine (0·30 c.c.) and adding acetic anhydride (0·25 c.c.). After 16 hours at 20°, excess of the reagents was removed under reduced pressure at 30°, and the product subjected to the usual washing of the ethereal solution with 2N-hydrochloric acid, 2N-sodium carbonate, and water, drying, and evaporation. The resultant oil was distilled in a molecular flask at 130—150° (bath temp.)/0·001 mm., but could not be induced to crystallise (Found: C, 71·72; H, 9·82. $C_{31}H_{52}O_6$ requires C, 71·50; H, 10·06%).

3(β)-*Hydroxycholestane-6||7-dicarboxylic Acid* 6 ⟶ 3-*Lactone* (XIV).—The hydroxy-acid (XIII) (50 mg.) was heated with pure acetic anhydride for 0·5 hour (cf. Lettré, *loc. cit.*); the product, obtained by complete evaporation in a vacuum, was dissolved in ether, and the ethereal solution washed thrice with 2N-sodium carbonate. Acidification of these alkaline extracts produced no turbidity, and subsequent extraction with ether failed to give a significant quantity of material. The foregoing ethereal solution was washed with water, dried, and evaporated to yield a colourless oil (37 mg.), which tended to separate from ether–pentane as a gel, but crystallised readily when rubbed with a trace of acetone. Recrystallisation from ether–pentane or methanol gave the lactonic acid as needles, m. p. 214—215°, resolidifying to a mass of needles at 210°. When dissolved in a little pure acetone, the substance titrated as a mono-basic acid with 0·01N-sodium hydroxide [Found: *M* (monobasic), 428. Calc. for $C_{27}H_{44}O_4$: *M*, 432·6]. The lactonic acid, when dissolved in ether, discharged the yellow colour of ethereal diazomethane with a brisk evolution of gas; after addition of excess of diazomethane and standing at 0° for 0·25 hour, the mixture was worked up in the usual manner to give the lactonic *methyl* ester as a colourless oil which could not be induced to crystallise before or after distillation at 150—160°/0·001 mm. (Found: C, 75·12; H, 10·36. $C_{28}H_{46}O_4$ requires C, 75·30; H, 10·36%). The ester crystallised after being kept for some months; to remove traces of colour and dust-particles, the material (40 mg.) was chromatographed over aluminium oxide (1·2 g.; Merck–Brockmann) in pentane, and the ester eluted with benzene–pentane (1 : 4, 3 × 4 c.c. and 1 : 3, 3 × 4 c.c.). These fractions were united and the ester twice crystallised from methanol to give fine, rectangular prisms (11 mg.), m. p. 104—105° (Found, after grinding and drying at 60°/0·01 mm.: C, 75·46; H, 10·38%). Another crystal-form from methanol, stout prisms, m. p. 96—97°, with transformation to long prismatic needles, m. p. 104°, was also observed.

An attempt to prepare the lactonic acid (XIV) using acetyl chloride for 3 hours (cf. Windaus and Stein, *loc. cit.*) gave a very small quantity of material non-extractable from ethereal solution with 2N-sodium carbonate; this crystallised from ether–pentane in flat plates, m. p. 188—190°, but was not further investigated. The bulk of material was precipitated by acidification of the alkaline extracts, and appeared to consist of unaltered hydroxy-acid (XIII).

Section (b).

Method (i) (with Dr. W. C. J. Ross).—*Methyl 7-keto-3(β)-acetoxy-5-allocholanate* (XXV; R′ = Ac, R″ = Me). Hydrogenation of 7-keto-3(β)-acetoxycholest-5-ene (XXII) with palladium in acetic acid (cf. Windaus and Kirchner, *Ber.*, 1920, **53**, 614; Barr, Heilbron, Jones, and Spring, *loc. cit.*) gave 7-keto-3(β)-acetoxycholestane (XXIII; R = Ac), m. p. 142—143°. This ketone (2·0 g.) was treated with a 2·7% solution of chromium trioxide in 90% acetic acid for 1 hour on the steam-bath; the cooled solution was diluted with sufficient water, extracted with ether, and the ethereal solution separated into neutral and acidic fractions by use of 2N-sodium carbonate. The acidic material (160 mg.), which solidified by

rubbing with methanol, was esterified with ethereal diazomethane at 0°, and the product acetylated by treatment with pyridine–acetic anhydride at 20° for 16 hours. The acetoxy-methyl esters (165 mg.) to obtained were dissolved in 0·5 c.c. of benzene and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV, 5 g.) prepared in pentane (25 c.c.). The column was eluted by the " durchlauf Methode " using eluates of 25 c.c. as shown in the table, the m. p.s recorded in which are subsequent to recrystallisation from methanol.

Fraction.	Eluant.	Eluate.
1—3	Pentane	Traces of oil
4	Benzene–pentane (1 : 10)	Much oil
5—7	,, ,, (1 : 5)	Some oil
8, 9	,, ,, (1 : 2·5)	,,
10	,, ,, (1 : 1)	Oil, inoculated with Fr. 13 but did not cryst.
11	,, ,, (1 : 1)	Crystallised spontaneously, m. p. 115—125°
12	,, ,, (1 : 1)	,, ,, m. p. 118—125
13	Benzene	,, ,, m. p. 130—133
14	,,	Cryst. by inoculation with Fr. 13, m. p. 131—134
15	,,	,, ,, ,, ,, m. p. 128—132
16, 17	,,	Traces of cryst. material, m. p. 120—126
18	Ether–benzene (1 : 1)	Little oil, failed to cryst. by inoculation
19	Ether	Trace of oil
20	,,	—

Fractions 11—17 were united (61 mg.) and recrystallised from methanol to give *methyl 7-keto-3(β)-acetoxy-5-allocholanate* (XXV; R′ = Ac, R″ = Me) (46 mg.) as prisms, m. p. 130—133° (Found,* after drying at 60°/0·01 mm.: C, 72·80; H, 9·92. $C_{27}H_{42}O_5$ requires C, 72·61; H, 9·50%). Hydrolysis of the ester with hot 4% methanolic potassium hydroxide (≡3 mols.), removal of methanol after saturation with carbon dioxide, and acidification yielded *3(β)-hydroxy-7-keto-5-allocholanic acid*, prisms from ether–pentane, m. p. 193° (Found,* after drying for 6 days at 75—80°/0·01 mm.: C, 73·74; H, 9·85. $C_{24}H_{38}O_4$ requires C, 73·80; H, 9·81%).

Subsequently, when it was found that methyl 3(β)-acetoxycholestane-6‖7-dicarboxylate was non-crystalline, Fractions 4—10 were subjected individually to alkaline hydrolysis; attempts to crystallise the various precipitates of acids obtained by acidification of the hydrolysates were uniformly unsuccessful.

Method (ii) (with Dr. N. Gough).—7-Keto-3(β)-benzoyloxycholestane (XXIII; R = Bz) (m. p. 159—160°, 4 g.) was dissolved in dioxan, and, to the mechanically stirred solution at 20°, solutions of iodine (7·3 g.) in methanol (90 c.c.) and potassium hydroxide (10 g.) in water (15 c.c.) plus methanol (35 c.c.) were added dropwise and simultaneously during 1·5 hours, iodine being always present in excess. After 0·5 hour at room temperature, the volume was reduced to about ½ under diminished pressure, and the solution diluted and extracted thrice with ether. The ethereal extract was shaken twice with N-sodium carbonate, and the united alkaline extracts acidified and re-extracted with ether; this extract, after being washed with sodium thiosulphate solution and water, was dried and evaporated. The residue by crystallisation from acetone–pentane gave benzoic acid, m. p. 120—121° (700 mg. = 73% hydrolysis of the starting material); the mother liquor by evaporation gave an intractable gum, which contained further small quantities of benzoic acid, but from which no other crystalline material could be isolated.

Method (iii). *3(β)-Hydroxy-6 : 7-diketocholestane* (XXVIII; R = H).—7-Keto-3(β)-acetoxycholestane (XXIII; R = Ac), m. p. 142—143°, was converted *via* 6″ *α* ″-bromo-7-keto-3(β)-acetoxycholestane (as XXIX), m. p. 175°, into 6″ *β* ″-bromo-7-keto-3(β)-acetoxycholestane (as XXIX), m. p. 143°, and the latter bromide (1 g.) oxidised with a boiling 10% solution of silver nitrate in pyridine (20 c.c.) for 2 hours to give 6 : 7-diketo-3(β)-acetoxycholestane (XXVIII; R = Ac), m. p. 156—157°, according to the procedure of Barr, Heilbron, Jones, and Spring (*loc. cit.*). The diketone so obtained was hydrolysed according to the following directions most kindly supplied by Dr. E. R. H. Jones: the acetoxy-diketone (400 mg.) was treated with 2% methanolic potassium hydroxide solution (30 c.c.) at 20° for 20 hours, and the resulting solution diluted with sufficient water, acidified with 2N-hydrochloric acid, and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate, then water, dried, evaporated, and the solid residue crystallised twice from methanol to give *3(β)-hydroxy-6 : 7-diketocholestane* as fine needles, m. p. 152—153° (Dr. Jones records m. p. 151·5—152·5°), giving an olive-green colour with ethanolic ferric chloride, which appear to contain 1 mol. of methanol (Found, § after drying at 100° in a vacuum for 8 hours: C, 75·3; H, 10·85. $C_{27}H_{44}O_3$,MeOH requires C, 75·0; H, 10·8%).

3(β)-Hydroxycholestane-6‖7-dicarboxylic acid (XIII).—The hydroxy-diketone (XXVIII; R = H) (200 mg.) was dissolved in hot ethanol (25 c.c.), and 30% hydrogen peroxide (0·6 c.c.) added, followed by 2N-potassium hydroxide (1·25 c.c.) (cf. Butenandt and Schramm, *Ber.*, 1936, **68**, 2298). The mixture was warmed on the steam-bath for 10 minutes, and kept at 20° for 16 hours. The colourless solution, after removal of ethanol under reduced pressure at 20°, was diluted and extracted with ether; the aqueous layer, after removal of dissolved ether under reduced pressure, was acidified with 2N-hydrochloric acid, and the precipitate filtered off and dried in a vacuum desiccator. The dry precipitate was dissolved in a little anhydrous dioxan (freshly distilled over sodium) and repeatedly evaporated under reduced pressure with successive amounts of dry benzene. The residue was recrystallised from acetone–pentane to give 3(β)-hydroxycholestane-6‖7-dicarboxylic acid (40 mg.) as aggregates of felted needles, m. p. 241—242° (gas evolution), undepressed by a genuine specimen of m. p. 241—242°, prepared by the method of Windaus and Stein (*loc. cit.*) (Found,* after drying at 100° for 3 hours without loss of weight in a weighing bottle: C, 71·63; H, 10·41. Calc. for $C_{27}H_{44}O_5$: C, 71·96; H, 10·30%). For further identification, the hydroxy-acid was converted into the lactonic acid (XIV); the hydroxy-acid (20 mg.) was heated with acetic anhydride for 0·5 hour and worked up as previously, and the lactonic acid, which

again was not extracted from ethereal solution with 2N-sodium carbonate, crystallised from ether–pentane; two crystalline forms were obtained—needles and clusters of prisms—both melting at 213—215° and re-solidifying to a mass of needles on cooling to 210°. The mixed m. p. with a genuine specimen of m. p. 214—215° showed no depression (m. p. 213—215°), whilst titration with 0·01N-potassium hydroxide confirmed the monobasic nature of the substance [Found: *M* (monobasic), 434. Calc. for $C_{27}H_{44}O_4$: *M*, 432·6], which also reacted vigorously with an ethereal solution of diazomethane.

The microanalyses (*) were performed in the micro-analytical laboratory of the Eidg. Techn. Hochschule, Zürich, through the kindness of Prof. L. Ruzicka, For. Mem. R.S.; the microanalyses (§) were carried out in 1937—1938 by the late Mr. Boston in the micro-analytical laboratory of Prof. Sir Ian Heilbron at the University of Manchester; other micro-analyses are by Dr. Weiler and Dr. Strauss of Oxford. The photographs (Figs. 1—4) were taken by Mr. Blackledge and Mr. J. Hainsworth at the University of Leeds.

The author wishes to record his gratitude to Dr. E. R. H. Jones for the gift of specimens and for making available his original laboratory note-books, and gratefully to acknowledge the support of the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund, and the Anna Fuller Fund.

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206. *Steroids and the Walden Inversion. Part IV. Derivatives of 6-Ketositostane and 6 : 17-Diketoandrostane.*

By C. W. SHOPPEE.

On the basis of the proven (β)-orientation of the hydroxyl group in "β"-sitosterol and dehydro*iso*androsterone (Part III, preceding paper), configuration at C_3 is now assigned to various derivatives of 6-ketositostane and 6 : 17-diketoandrostane.

IN Part I (*J.*, 1946, 1138), configurations were assigned to the epimeric 3-chlorositostanes * which undergo bimolecular acetolysis (mechanism S_N2) to give respectively sitostanol and *epi*-sitostanol: the "β"-chloride, m. p. 118°, is 3(α)-chlorositostane, and the "α"-chloride, m. p. 108°, is 3(β)-chlorositostane. In Part II (*J.*, 1946, 1147) it was suggested that preservation of configuration in nucleophilic substitution reactions at C_3 in 5 : 6-unsaturated steroids was due to the intervention of the polarisable electrons of the double bond, which not only facilitate separation of the atom or group replaced at C_3 as the anion so that reaction occurs by mechanism S_Ni, but also interact with the resulting positive charge at C_3 to maintain configuration in the intermediate cation. Experimental support for the correctness of this suggestion has recently been given by Winstein and Adams (*J. Amer. Chem. Soc.*, 1948, **70**, 838) who have shown that acetolysis of cholesteryl *p*-toluenesulphonate at 50° occurs by mechanism S_Ni.

In Part III (preceding paper) it was proved that the hydroxyl group in "β"-sitosterol (I) and dehydro*iso*androsterone (as I) is (β)-orientated, and on this basis, consideration is now extended to derivatives of these two substances.

"β"-Sitosterol (I) by treatment with phosphorus pentachloride gives sitosteryl chloride (Burian, *Monatsh.*, 1897, **18**, 551; Vanghelovici and Angelescu, *Bul. Soc. Chim. România*, 1935, **17**, 184; Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711) which is 3(β)-chlorositost-5-ene (II),† since catalytic reduction gives a quantitative yield of 3(β)-chlorositostane (V), m. p. 108° (Marker and Lawson, *loc. cit.*). The same sitosteryl chloride (II) is now found to be obtained by use of thionyl chloride alone or in the presence of pyridine, so that here again the steric course of the replacement of the hydroxyl group by chlorine is independent of the reagent within the range of reagents and conditions examined.

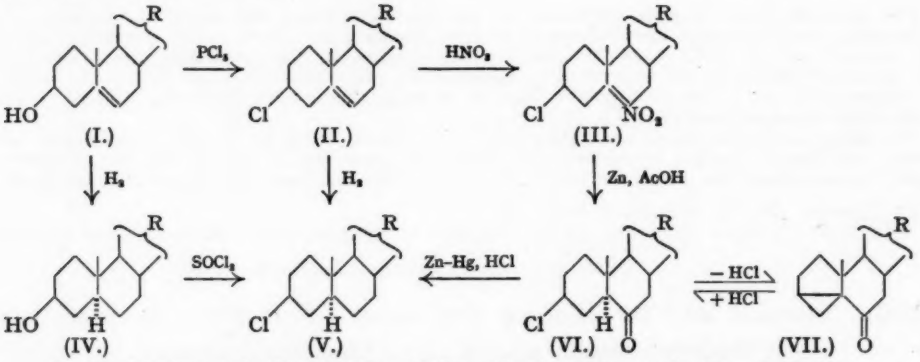
Nitration of sitosteryl chloride (II) in the presence of nitrite yields 3(β)-chloro-6-nitrositost-5-ene (III), which by reduction with zinc and acetic acid gives a chloro-ketone, m. p. 112°, which is 3(β)-chlorositostene-6-one (VI). This structure is consistent with its reduction by the Clemmensen method (Vanghelovici and Angelescu, *loc. cit.*) to the sitostanyl chloride, m. p. 108°, which has been shown to be 3(β)-chlorositostane (V) since it is obtained from sitostanol (IV) by treatment with thionyl chloride (retention of configuration) and from *epi*sitostanol by use of phosphorus pentachloride (inversion of configuration) (Part I, *loc. cit.*). The chloro-acid, m. p. 277°, obtained by Vanghelovici and Angelescu (*loc. cit.*) by oxidation of 3(β)-chlorositostan-6-one (V) with nitric acid is clearly 3(β)-chlorositostane-6‖7-dicarboxylic acid.

Whilst *i*-sterols and their derivatives will be dealt with in a future paper it is however

* Also termed 3-chlorostigmastanes.

† The sitosteryl bromide obtained by Vanghelovici and Vasiliu (*Bul. Soc. Chim. România*, 1935, **17**, 251) from "β"-sitosterol by use of phosphorus tribromide is analogously 3(β)-bromositost-5-ene.

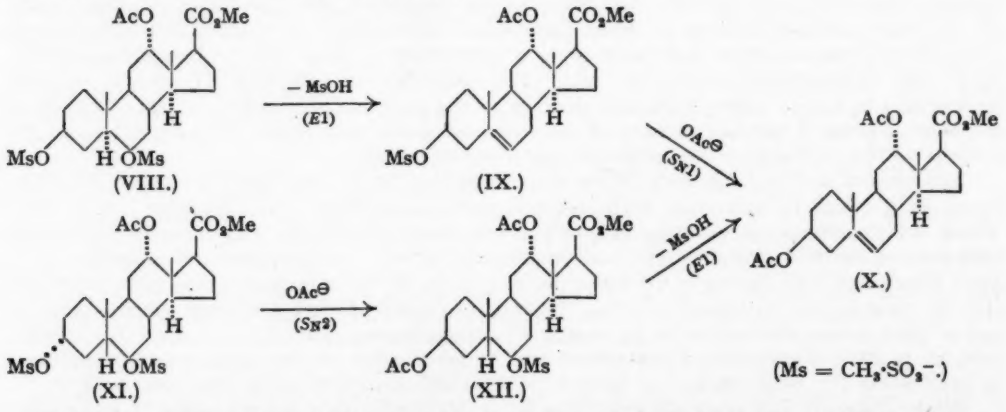
appropriate here to indicate that the substance, m. p. 77°, obtained by Vanghelovici and Angelescu from 3(β)-chlorositostan-6-one (VI) by treatment with sodium amalgam in boiling ethanol and described by them as sitostan-6-one, is actually *i*-sitostan-6-one (VII) since it is readily obtained from the chloro-ketone (VI) by sublimation in a vacuum and is reconverted into (VI) by the action of hydrochloric acid.



In the sitostane series R = $C_{19}H_{34}$; in the androstan-17-one series R = $C_8H_{12}O$.

In the androstane series, compounds analogous to the foregoing have been described to which configuration at C_3 can now be assigned. 3(β)-Hydroxyandrost-5-en-17-one (dehydro*iso*androsterone) (I) by treatment with phosphorus pentachloride (1 mol.), thionyl chloride, or hydrochloric acid gives uniformly 3(β)-chloroandrost-5-en-17-one, m. p. 157° (II), with retention of configuration, since by hydrogenation this yields 3(β)-chloroandrostan-17-one, m. p. 173° (V) (cf. Part II, *loc. cit.*); it follows that the quantities of the chloro-ketone (II) isolated from male urine by Butenandt and Dannenbaum (*Z. physiol. Chem.*, 1934, **229**, 185; with Hanisch and Kudszus, *ibid.*, 1935, **237**, 57) and encountered in pathological urines by other workers, represent equivalent quantities of dehydro*iso*androsterone (I), originally excreted as such or as a conjugate, *e.g.*, with glucuronic acid, and converted into (II) during hydrochloric acid hydrolysis of the urine.

Nitration of the unsaturated chloro-ketone (II) gives 3(β)-chloro-6-nitroandrost-5-en-17-one (III) (Blunschy, Hardegger, and Simon, *Helv. Chim. Acta*, 1946, **29**, 199), reduced by zinc and acetic acid to 3(β)-chloroandrostane-6 : 17-dione (VI). Analogy suggests that the bromodiketone described by Butenandt and Suranyi (*Ber.*, 1942, **75**, 591) is 3(β)-bromoandrostane-6 : 17-dione (as VI); these authors obtained it from *i*-androstane-6 : 17-dione (VII) in quantitative yield by treatment with hydrobromic acid in acetic acid at 20°, and showed that removal of the elements of hydrogen bromide by use of hot collidine or with potassium acetate in acetic acid regenerated *i*-androstane-6 : 17-dione (VII).



Reference may here be made to a remarkable experimental result recently recorded by Lardon (*Helv. Chim. Acta*, 1947, **30**, 597, especially 604). The 3(β) : 6-dimethanesulphonyl ester of the androstane derivative (VIII) by treatment with silver acetate in hot acetic acid yields the

3(β)-acetoxyandrost-5-ene derivative (X) with retention of configuration at C_3 (Jeanloz, Prins, and von Euw, *ibid.*, 1947, **30**, 374); this result clearly indicates that the first stage in the transformation is the elimination by mechanism *E*1 of methanesulphonic acid to give (IX), which, by virtue of the 5 : 6-double bond so introduced, undergoes unimolecular acetolysis of the 3(β)-methanesulphonyl group (mechanism S_N1) with preservation of configuration at C_3 to yield the 3(β)-acetoxyandrost-5-ene compound (X).

The isomeric 3(α) : 6-dimethanesulphonyl ester of the ætiocholane derivative (XI) by treatment with silver acetate in hot acetic acid yields the same 3(β)-acetoxyandrost-5-ene derivative (X) with inversion of configuration at C_3 (Lardon, *loc. cit.*). This result indicates equally clearly that here the primary reaction is a bimolecular acetolysis (mechanism S_N2) of the saturated ester (XI) to give with inversion the saturated 3(β)-acetoxy-6-methanesulphonyl ester (XII), which subsequently eliminates the elements of methanesulphonic acid (mechanism *E*1) to produce the unsaturated 3(β)-acetoxy-compound (X).

If *trans*-elimination, being the rule (cf. Watson, "Modern Theories of Organic Chemistry", 2nd Ed., 1941, p. 223), is the more facile process, these results suggest that in (VIII) the 6-methanesulphonyl group is (β)-orientated (C_5–H/C_6–OMs : *trans*), whilst in (XI) the 6-methanesulphonyl group is also (β)-orientated (C_5–H/C_6–OMs : *cis*), so that the elimination reaction takes preference over the substitution reaction in the conversion (VIII) ⟶ (X) but that the situation is reversed in the conversion (XI) ⟶ (X).

Experimental.

Commercial sitosterol (1 g.) was added to redistilled thionyl chloride (3 c.c.), and the clear solution left for 10 minutes at room temperature; the resulting pink solution was poured into ice-cold N-sodium carbonate, and the precipitate filtered off and well washed with water. The precipitate was stirred with successive quantities of warm pentane, in which it largely dissolved, and the united pentane extracts filtered through a column of aluminium oxide (Spence, activity I—II, 30 g.) prepared in pentane. The column was eluted twice with pentane (100 c.c.); the original filtrate and these eluates by evaporation gave residues which crystallised spontaneously. The crystallisates all melted at 87—88°, and were united and recrystallised from acetone to give pure 3(β)-chlorositost-5-ene (200 mg.) as prisms, m. p. 88—89°. The same compound was obtained by carrying out the reaction in the presence of pyridine (cf. Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665), and gave no depression with a specimen prepared using phosphorus pentachloride.

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207. *Purpurogallin. Part I.*

By Robert D. Haworth, Barry P. Moore, and Peter L. Pauson.

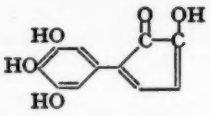
The reduction of purpurogallin and its tri- and tetra-methyl ethers has been examined. Oxidation of tetramethyl tetrahydropurpurogallin with alkaline hydrogen peroxide has yielded a dibasic acid identical with γ-(3 : 4 : 5-trimethoxy-2-carboxyphenyl)butyric acid (X) which has been synthesised; the isomeric γ-(2 : 3 : 4-trimethoxy-6-carboxyphenyl)butyric acid (IX) has also been synthesised. The identification of (X) establishes structure (VI; R = Me) for tetramethyl tetrahydropurpurogallin and supports the benz*cyclo*heptatrienolone structure (III) for purpurogallin.

Further evidence supporting structure (III) is obtained from the atmospheric oxidation of alkaline solutions of purpurogallin which results in the rupture of the benzenoid ring and the formation of the acid (XV; R = H). This acid (XV; R = H) and its decarboxylation product, 2-hydroxy-6-methyl*cyclo*heptatrienone (XVI) closely resemble stipitatic acid in properties.

The mechanism of the conversion of pyrogallol into purpurogallin is discussed.

Purpurogallin, $C_{11}H_8O_5$, which is obtained by oxidation of pyrogallol in a variety of ways, has been the subject of numerous investigations which are adequately summarised in the important contribution of Willstätter and Heiss (*Annalen*, 1923, **433**, 17). As a result of an ingenious theoretical treatment, these authors advanced structure (I) for purpurogallin, and this structure appears to have been widely accepted. The evidence discussed by the proposers is, however, not by any means conclusive, and recently several chemists in this country have shown an interest in the problem and considered alternative structures. During the course of lectures given to the Chemical Societies at Imperial College and Bangor in 1943, one of us suggested the

quinonoid formula (II), and similar ideas had occurred to Professor Wilson Baker (private communication, December 3rd, 1945). Professor J. W. Cook also informs us (private



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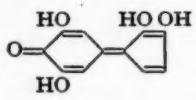

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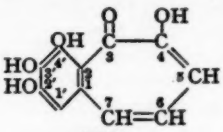
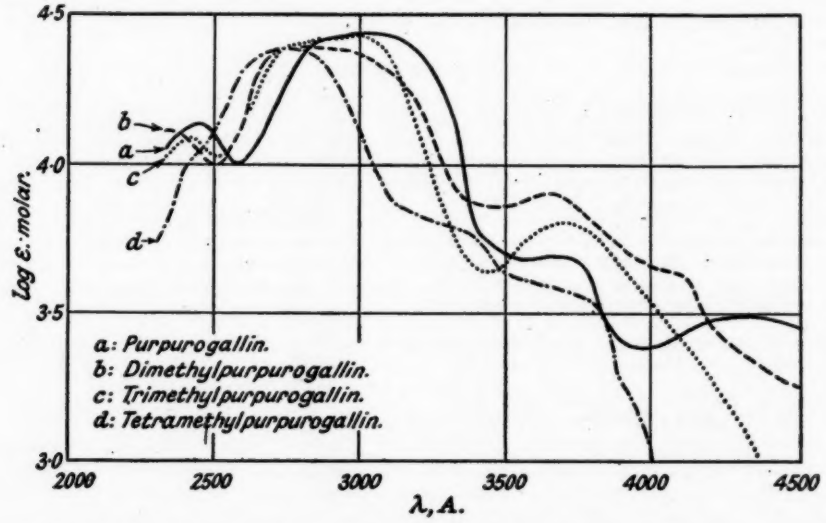


(III.)

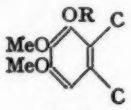
communication, June 17th, 1947) that Dr. J. D. Loudon had considered the benz*cyclo*heptatrienolone structure (III) and that some preliminary reduction experiments were carried out in 1945 by Dr. Loudon and Mr. J. Robertson. Recently, Barltrop and Nicholson have submitted a paper on purpurogallin for publication, and Dr. J. A. Barltrop has informed us (private communication, May 24th, 1947) that they have established the structure (IV; R = Me) in tetramethylpurpurogallin, and suggested that the trimethyl ether contains the phenolic structure (IV; R = H) and, in addition, they have adduced theoretical reasons in favour of structure (III) for purpurogallin.



In order to obtain further experimental evidence bearing on the problem, an investigation involving reduction, methylation, and oxidation of purpurogallin was planned, and the synthesis of some of these derivatives was commenced in 1943. Certain aspects of this work are at present incomplete, but in view of the work of Barltrop and Nicholson it is desirable that some of our results, which provide very strong experimental evidence in favour of structure (III), should be described and interpreted in terms of this structure.

Catalytic hydrogenation of purpurogallin yielded the yellow *tetrahydropurpurogallin*, but, as the reduction was very slow and the results erratic, this approach was soon abandoned in favour of experiments in which methylation preceded reduction. When purpurogallin was methylated in dioxan solution with excess of diazomethane, the yellow trimethyl purpurogallin (V; R = H), prepared by earlier investigators, was obtained. Methylation with a limited amount of diazomethane gave an orange *dimethyl purpurogallin* which was converted into the trimethyl ether (V; R = H) by further methylation. The colourless alkali-insoluble tetramethyl purpurogallin (V; R = Me) was prepared by the action of methyl sulphate on a solution of the trimethyl ether (V; R = H) in concentrated sodium hydroxide. The reduction in colour and the use of concentrated alkali during the methylation suggested, at one time, that structural modification may be associated with the introduction of the fourth methyl ether group, but a comparison of the absorption spectra of purpurogallin and its di-, tri-, and tetra-methyl ethers (see Fig.) indicates that profound structural change is very unlikely. In addition it was found that tetramethyl purpurogallin (V; R = Me) was quantitatively converted into the trimethyl ether by warming for a few minutes with 2N-hydrochloric acid. This ready hydrolysis

and the absence of ketonic properties in purpurogallin and its di-, tri-, and tetra-methyl ethers is noteworthy.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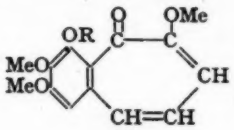
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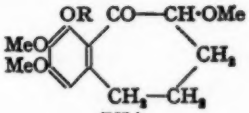
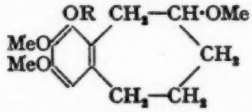
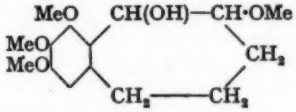
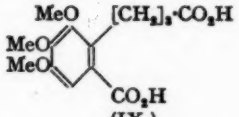

(VI.)

Attempts to oxidise tri- and tetra-methyl purpurogallin under a variety of conditions failed to yield recognisable products, and reduction processes were investigated. Trimethyl purpurogallin is readily reduced to colourless phenolic ketones by the action of amalgamated zinc and acids, and it is hoped to describe these products when the constitutions have been elucidated more fully. Trimethyl purpurogallin is not easily hydrogenated in the presence of palladium catalysts, but was readily reduced with Adams's platinum catalyst. The product was always a mixture the nature of which was very dependent on the activity of the catalyst and the nature of the solvent employed. Hydrogenation in acetic acid with freshly prepared catalyst gave an oil which was resolved by Girard-T into *trimethyl tetrahydropurpurogallin* (VI; R = H), giving a 3 : 5-*dinitrobenzoate* and a 2 : 4-*dinitrophenylhydrazone*, and *trimethyl hexahydrodeoxypurpurogallin* (VII; R = H) which had no ketonic properties but gave a *methyl ether* (VII; R = Me). With the same catalyst but with ethanol as solvent the proportion of ketonic phenol (VI; R = H) was increased, and the same result was achieved by the use of a less active catalyst in acetic acid. With a less active catalyst in ethanol reduction was very slow, and the product, a ketonic *phenol* (A), $C_{14}H_{18}O_5$, which gave a 3 : 5-*dinitrobenzoate*, resembled the isomeric ketonic phenol (VI; R = H) very closely except that the 2 : 4-dinitrophenylhydrazone was

(VII.) 


(VIII.)

amorphous. The relationship between the two isomers is not understood, but the production of these phenolic reduction products indicates the presence of one phenolic group in the benzene nucleus of trimethyl purpurogallin or alternatively suggests a quinonoid structure such as (II) for purpurogallin. Methylation of trimethyl tetrahydropurpurogallin (VI; R = H) afforded *tetramethyl tetrahydropurpurogallin* (VI; R = Me) as an oil giving a 3 : 4-*dinitrophenylhydrazone*, and the same tetramethyl ether was obtained together with *tetramethyl hexahydropurpurogallin* (VIII) by reducing tetramethyl purpurogallin with Adams's catalyst in ethanol. Tetramethyl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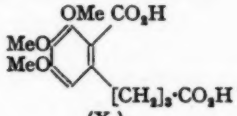
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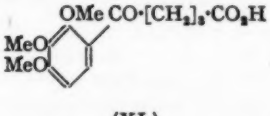
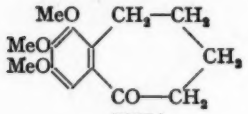
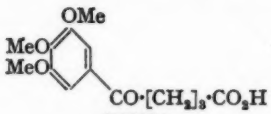

(XI.)

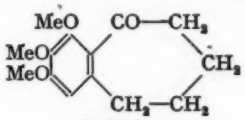
tetrahydropurpurogallin (VI; R = Me) was readily oxidised by alkaline hydrogen peroxide to a dibasic acid which did not give a cyclic anhydride or imide. The properties suggested a γ-(*o*-carboxyphenyl)butyric acid structure, and, after some experiments involving the Wieland method of degrading carboxylic acids had failed to give useful information, the synthesis of the acids (IX) and (X) was undertaken and led to the exclusion of (IX) and the establishment of structure (X) for the dibasic acid.

Condensation of glutaric anhydride with pyrogallol trimethyl ether in the presence of aluminium chloride yielded a mixture of γ-(2 : 3 : 4-*trimethoxybenzoyl*)*butyric acid* (XI) and a γ-(*hydroxydimethoxybenzoyl*)*butyric acid*. Clemmensen reduction of (XI) or the demethylated product in toluene solution yielded a δ-(*hydroxydimethoxyphenyl*)*valeric acid* which was methylated to give δ-(2 : 3 : 4-*trimethoxyphenyl*)*valeric acid*. Cyclisation with phosphoric oxide in benzene afforded 1′ : 2′ : 3′-*trimethoxybenz*cyclo*hepten*-3-*one* (XII) as an oil giving a crystalline 2 : 4-*dinitrophenylhydrazone*. The cyclic ketone (XII) was oxidised first with selenium dioxide to the α-diketone which was not isolated, the crude diketone being converted by means of alkaline hydrogen peroxide into γ-(2 : 3 : 4-*trimethoxy*-6-*carboxyphenyl*)*butyric acid* (IX). For the synthesis of the isomeric acid (X), ethyl γ-(3 : 4 : 5-trimethoxybenzoyl)acetate and ethyl β-iodopropionate were condensed and the resulting oil was hydrolysed by 20% sulphuric acid to

γ-(3 : 4 : 5-*trimethoxybenzoyl*)*butyric acid* (XIII). The acid (XIII) was reduced by Minlon's modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the Wolff–Kishner method to


(XII.)

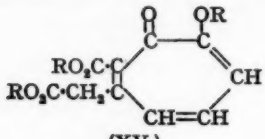

(XIII.)

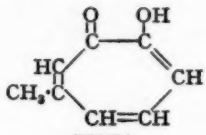

(XIV.)

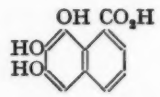
δ-(3 : 4 : 5-*trimethoxyphenyl*)*valeric acid*, which was cyclised by phosphoric oxide in benzene to 2′ : 3′ : 4′-*trimethoxybenz*cyclo*hepten*-3-*one* (XIV). Successive oxidations with selenium dioxide and hydrogen peroxide proceeded smoothly to give the required *γ*-(3 : 4 : 5-*trimethoxy*-2-*carboxyphenyl*)*butyric acid* (X), which had m. p. 146—147° and was identical with the dibasic acid, m. p. 146—147°, obtained by oxidising tetramethyl tetrahydropurpurogallin as described above.

The elucidation of the structure of the dibasic acid proves that tetramethyl tetrahydropurpurogallin has the 4 : 2′ : 3′ : 4′-tetramethoxybenz*cyclo*hepten-3-one structure (VI; R = Me) and definitely excludes phenyl*cyclo*pentadiene structures such as (I) and (II), and naphthalene formulae such as that advocated by Dean and Nierenstein (*Ber.*, 1913, **46**, 3868).

In addition, important evidence supporting the presence of the *cyclo*heptatrienolone ring in purpurogallin has been obtained by examining the action of air on an alkaline solution of the pigment. Much humic acid was produced, but continuous ether extraction led to the isolation of 5% yields of a tribasic acid, $C_{10}H_8O_6$, probably 4-*hydroxy*-3-*keto*-2-*carboxy*cyclo*heptatrienyl*-


(XV.)


(XVI.)


(XVII.)

acetic acid (XV; R = H), which was very soluble in water, gave a yellow sodium salt and a red ferric test, did not react with 2 : 4-dinitrophenylhydrazine, and with diazomethane yielded the neutral *trimethyl* derivative (XV; R = Me). When heated above the melting point, (XV; R = H) was converted into 2-*hydroxy*-6-*methyl*cyclo*heptatrienone* (XVI) which dissolved in sodium hydrogen carbonate solution, gave a green ferric test, but did not react with 2 : 4-dinitrophenylhydrazine. Catalytic reduction of (XVI) resulted in the absorption of 3·5 mols. of hydrogen and the formation of a neutral oil which gave an amorphous 2 : 4-dinitrophenylhydrazone. These substances are being further investigated, but their properties closely resemble those recorded by Birkenshaw, Chambers, and Raistrick (*Biochem. J.*, 1942, **36**, 242) for stipitatic acid, for which Dewar (*Nature*, 1945, **155**, 50) has suggested a *cyclo*heptatrienolone structure, and the rupture and removal of the phenolic ring is interesting in connection with the biogenetic suggestions advanced previously (Tilden lecture, *J.*, 1942, 456) by one of us.*

The conversion of pyrogallol into the benzotropolone (Dewar, *loc. cit.*) system (III) can be readily accommodated by a slight modification of the suggestions of Willstätter and Heiss (*loc. cit.*). These authors assume the production of 3 : 4 : 5 : 2′ : 3′ : 4′-hexahydroxydiphenyl followed by oxidation and benzilic rearrangement to (I) by (*a*) union of carbon atoms in positions 1′ and 3′, (*b*) the rupture of the bond between carbon atoms 1′ and 2′, and (*c*) elimination of carbon dioxide. The benzotropolone structure (III) may be derived similarly by retaining the changes (*b*) and (*c*) but postulating union of carbon atom 3′ with carbon atom 2 instead of with carbon atom 1′; such a modification is reasonable in view of the conjugation of positions 2 and 1′.

Experiments on the mechanism of this reaction have been initiated, and it is hoped to publish shortly the results of synthetical experiments which aim at the synthesis of purpurogallone (XVII). This structure (XVII), suggested by Perkin (*J.*, 1903, **83**, 192; 1912, **101**, 803), is readily derived by further benzilic acid change from the benzotropolone structure (III).

* *Added July 2nd*, 1948.—The isolation of three isomeric *iso*propyl*cyclo*heptatrienolones from Western red cedar (Erdtman and Gripenberg, *Nature*, 1948, **161**, 719) is interesting; these probably arise from the corresponding pyrogallols by oxidation to purpurogallin analogues and subsequent fission of the benzene nucleus.

Experimental.

Purpurogallin, obtained in 60% yields from pyrogallol by oxidation with potassium iodate as described by Evans and Dehn (*J. Amer. Chem. Soc.*, 1939, **52**, 3647), was purified either by sublimation in a vacuum * (4 mm.), or by crystallisation from a mixture of equal parts of phenol and glacial acetic acid. It was isolated as red prisms or plates, m. p. 276° (decomp.) (Found: C, 60·0; H, 3·8. Calc. for $C_{11}H_8O_5$: C, 60·0; H, 3·6%), which did not react with ketonic reagents; it was readily reduced by zinc and dilute hydrochloric acid to colourless ill-defined amorphous products.

Tetrahydropurpurogallin. Finely powdered purpurogallin (1 g.) was suspended in acetic acid (50 c.c.) and hydrogenated over Adams's catalyst (20 mg.) until hydrogen absorption ceased (24 hours; approximately 2·8 mols. of hydrogen were absorbed). Evaporation yielded *tetrahydropurpurogallin* which separated from acetic acid in yellow laminæ, m. p. 232—233° (decomp.) (Found: C, 58·9; H, 5·4. $C_{11}H_{12}O_5$ requires C, 59·0; H, 5·4%), which dissolved in aqueous alkali to a stable yellow solution.

Dimethyl Purpurogallin.—Purpurogallin (5 g.) in dioxan (200 c.c.) was treated with an ethereal solution of diazomethane prepared (by distillation) from *N*-nitrosomethylurethane (13·5 c.c.). After 12 hours the mixture was evaporated, finally in a vacuum, and the residue crystallised from ethanol. *Dimethylpurpurogallin* separated in orange needles (4 g.), m. p. 156° (Found: C, 62·7; H, 5·1; OMe, 24·5. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8; OMe, 25·0%), which dissolved in aqueous alkali to a stable yellow-orange solution. A Zerewitinoff determination in anisole solution indicated two active hydrogen atoms per molecule.

Trimethyl Purpurogallin (V; R = H).—Purpurogallin (16 g.) in dioxan (40 c.c.) was treated with diazomethane (20% excess) in ether (1200 c.c.). After 1 hour, ligroin (400 c.c.) was added; the trimethyl ether which gradually separated was collected after 48 hours and crystallised from ethanol. Yellow needles (15 g.), m. p. 176°, were obtained and a further small crop (1 g.) was obtained from the mother liquors. A Zerewitinoff determination showed the presence of one active hydrogen atom per molecule. The 3 : 5-*dinitrobenzoate*, prepared in pyridine, crystallised from acetic acid in yellow plates, which decomposed to a dark red liquid at 260° (Found: C, 55·1; H, 3·4; N, 6·5; OMe, 20·2. $C_{21}H_{16}O_{10}N_2$ requires C, 55·3; H, 3·5; N, 6·1; OMe, 20·4%).

Tetramethyl Purpurogallin (V; R = Me).—Methyl sulphate (3 c.c.) was added with shaking to a suspension of finely powdered trimethyl purpurogallin (1 g.) in 65% potassium hydroxide (15 c.c.). The mixture was warmed to initiate the vigorous reaction which then proceeded to completion without further attention. The cooled mixture was diluted with water and acidified. The *tetramethyl ether*, which separated as an oil, rapidly solidified, and crystallised from *cyclo*hexane in colourless plates, m. p. 94°, which did not react with ketonic reagents. A Zerewitinoff determination showed the absence of active hydrogen. The tetramethyl ether (0·1 g.) and 2N-hydrochloric acid (5 c.c.) were warmed on a water-bath until the colourless solution assumed a deep orange colour (5 minutes); on dilution with water, trimethylpurpurogallin, m. p. 173—175° (80 mg.), separated.

Catalytic Reduction of Trimethyl Purpurogallin.—(*a*) Trimethyl purpurogallin (4 g.) was suspended in acetic acid (100 c.c.) and hydrogenated at 15° and ordinary pressure in the presence of freshly prepared Adams's catalyst (10 mg.). After 2·5 hours, when 950 c.c. of hydrogen had been absorbed, the product was distilled to give an oil (2·7 g.), b. p. 160—170°/0·03 mm. This oil was dissolved in ethanol (20 c.c.) and acetic acid (2 c.c.), warmed for 1 hour with Girard's reagent-T (1 g.), diluted with water, and freed from non-ketonic material by extraction with ether. Removal of the ether yielded 4′-*hydroxy*-4 : 2′ : 3′-*trimethoxybenz*cyclo*heptene* (*trimethyl hexahydrodeoxypurpurogallin*) (VII; R = H), which separated from *cyclo*hexane in pale cream prisms, m. p. 82° (Found: C, 66·8; H, 7·6. $C_{14}H_{18}O_4$ requires C, 66·7; H, 7·9%). Methylation with methyl sulphate and alkali yielded 4 : 2′ : 3′ : 4′-*tetramethoxybenz*cyclo*heptene* (VII; R = Me), which crystallised from aqueous methanol in colourless prisms, m. p. 75—76° (Found: C, 67·7; H, 8·2; OMe, 46·1. $C_{15}H_{22}O_4$ requires C, 67·8; H, 8·3; OMe, 46·6%). The aqueous liquor from the above ether extraction was heated for 1 hour with concentrated hydrochloric acid (10 c.c.); ether then removed 4′-*hydroxy*-4 : 2′ : 3′-*trimethoxybenz*cyclo*hepten*-3-*one* (*trimethyl tetrahydropurpurogallin*) (VI; R = H), which separated from *cyclo*hexane in colourless prisms (0·3 g.), m. p. 86—87° (Found: C, 63·5; H, 6·8. $C_{14}H_{16}O_5$ requires C, 63·2; H, 6·8%), and gave a 3 : 5-*dinitrobenzoate* as yellow prisms, m. p. 161—162° (Found: C, 54·5: H, 4·5; N, 6·4. $C_{21}H_{20}O_{10}N_2$ requires C, 54·8; H, 4·4; N, 6·1%), from ethanol, and a 2 : 4-*dinitrophenylhydrazone*, crystallising from ethanol in deep yellow prisms, m. p. 204° (Found: C, 54·0; H, 5·0; N, 13·0. $C_{20}H_{22}O_8N_4$ requires C, 53·8; H, 4·9; N, 12·6%). This ketonic phenol (VI; R = H) was converted by methyl sulphate and sodium hydroxide into 4 : 2′ : 3′ : 4′-*tetramethoxybenz*cyclo*hepten*-3-*one* (*tetramethyl tetrahydropurpurogallin* (VI; R = Me), an oil, b. p. 140—145°/0·5 mm. (Found: C, 64·6; H, 7·2; OMe, 44·0. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1; OMe, 44·3%), giving a 2 : 4-*dinitrophenylhydrazone* which crystallised from ethanol in yellow needles, m. p. 176° (Found: C, 54·6; H, 5·4; N, 12·5. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·2; N, 12·2%).

(*b*) Trimethyl purpurogallin (8·6 g.) suspended in ethanol (250 c.c.) was reduced in presence of freshly prepared Adams's catalyst (0·1 g.). After 48 hours, when 2200 c.c. of hydrogen had been consumed, the product was isolated by distillation as an oil (5·5 g.), b. p. 170—180°/0·4 mm., from which (VI; R = H) (3·3 g.), m. p. 84°, rapidly separated. The residual oil was separated by Girard-T reagent into the ketonic phenol (VI; R = H) (0·6 g.) and (VII; R = H) (1·3 g.), m. p. 82°, as described in (*a*).

(*c*) Trimethyl purpurogallin (1 g.) was suspended together with Adams's catalyst (10 mg., prepared 2 months previously) in ethanol (60 c.c.). After 48 hours, when 240 c.c. of hydrogen had been absorbed, the ketonic phenol (A) was isolated as an oil, b. p. 145—150°/0·01 mm., which rapidly solidified and crystallised from *cyclo*hexane in cream-coloured prisms, m. p. 87° (Found: C, 63·4; H, 6·9; OMe, 34·5. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8; OMe, 35·0%). A Zerewitinoff determination showed the presence of one active hydrogen atom per molecule. The ketonic phenol (A) gave a 3 : 5-*dinitrobenzoate*

* Professor W. Baker kindly drew our attention to this method of purification, which had been used by Miss J. D. Hayward.

which crystallised from ethanol in yellow plates, m. p. 168° (Found: C, 54·9; H, 4·5; N, 6·5. $C_{21}H_{20}O_{10}N_2$ requires C, 54·8; H, 4·4; N, 6·1%), and an amorphous 2 : 4-dinitrophenylhydrazone.

Catalytic Reduction of Tetramethyl Purpurogallin.—Tetramethyl purpurogallin (0·4 g.) was reduced in ethanol (20 c.c.) in presence of freshly prepared Adams's catalyst (10 mg.). After 10 hours, when 100 c.c. of hydrogen had been absorbed, the product was distilled, and the oil, b. p. 120—130°/0·005 mm. (0·25 g.), deposited 4 : 2′ : 3′ : 4′-*tetramethoxybenz*cyclo*hepten*-3-*ol* (*tetramethyl hexahydropurpurogallin*) (VIII) on trituration with ether; crystallisation from acetone–ligroin gave colourless prisms, m. p. 142—143° (Found: C, 63·6; H, 8·0. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8%), which yielded a crystalline 3 : 5-*dinitrobenzoate*, m. p. > 250°. The mother liquors from the carbinol yielded on evaporation tetramethyl tetrahydropurpurogallin (VI; R = Me) which was identified as the 2 : 4-dinitrophenylhydrazone, m. p. 176°, described on page 1049.

Oxidation of Tetramethyl Tetrahydropurpurogallin (VI; R = Me).—The ketonic ether (VI; R = Me) (1·8 g.) was dissolved in ethanol (30 c.c.), mixed with a solution of sodium hydroxide (3 g.) in water (9 c.c.), and heated on the water-bath for 1 hour with hydrogen peroxide (25 c.c. of 20 vol.). The mixture was cooled, neutral impurities were removed in ether, and, after acidification, γ-(3 : 4 : 5-*trimethoxy*-2-*carboxyphenyl*)*butyric acid* (X) was isolated with ether and crystallised from acetone–ligroin; colourless prisms (1·6 g.), m. p. 146—147° (Found: C, 56·0; H, 6·0; equiv., 150. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·0%; equiv., 149), were obtained. The *dimethyl* ester (4·2 g.) of (X), prepared by the use of ethereal diazomethane as an oil, b. p. 170—180°/0·4 mm., was dissolved in ether (10 c.c.) and added to a solution of methylmagnesium iodide, prepared from magnesium (2·9 g.), methyl iodide (8·5 c.c.) and ether (80 c.c.). After 1 hours' refluxing, the resulting carbinol was isolated and heated with potassium hydrogen sulphate (10 g.) and potassium sulphate (0·5 g.) at 180° for ½ hour. The product, isolated with ether, was separated by distillation into approximately equal quantities of two fractions, b. p. 150—155°/0·4 mm. and b. p. 165—170°/0·4 mm. respectively, which rapidly decolourised bromine in chloroform solution. The fraction, b. p. 165—170°/0·4 mm. (1 g.) was ozonised at − 78° in ethyl acetate (30 c.c.) for ½ hour; a crystalline *aldehyde* separated and crystallised from acetone–ligroin in colourless prisms, m. p. 111° (Found: C, 58·1; H, 6·1. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%), which reduced Tollens's reagent and gave a 2 : 4-*dinitrophenylhydrazone* which crystallised from ethyl acetate in orange prisms, m. p. 196° (Found: C, 51·2; H, 4·6. $C_{19}H_{20}O_9N_4$ requires C, 50·9; H, 4·5%). This aldehyde has not been identified, and ozonisation of the fraction, b. p. 150—155°/0·4 mm., did not yield recognisable products.

Synthesis of γ-(3 : 4 : 5-*Trimethoxy*-2-*carboxyphenyl*)*butyric Acid* (X).—γ-(3 : 4 : 5-*Trimethoxybenzoyl*)-*butyric acid* (XIII). Ethyl β-iodopropionate (4·2 g.) was added with constant swirling to an ice-cold solution of the sodio-derivative prepared from ethyl 3 : 4 : 5-trimethoxybenzoylacetate (4·2 g.) (Perkin and Weizmann, *J.*, 1906, **89**, 1655), sodium (0·5 g.), and ethanol (40 c.c.). After 1 hour at 0° and 12 hours at 15°, the mixture was diluted with water, and the product, isolated with ether, was refluxed for 48 hours with 20% sulphuric acid (40 c.c.). Ice cooling deposited a crude acid which was taken up in dilute sodium hydroxide solution, neutral impurities were removed in ether, and the recovered *acid* (XIII) (4·2 g.) crystallised from benzene–ligroin in colourless plates, m. p. 120—121° (Found: C, 59·7; H, 6·1. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). The *methyl* and the *ethyl* ester crystallised from ligroin in stout prisms, m. p. 60—61° (Found: C, 60·7; H, 7·0. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%) and m. p. 68° (Found: C, 62·3; H, 7·0. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%) respectively.

δ-(3 : 4 : 5-*Trimethoxyphenyl*)*valeric acid.* The keto-acid (XIII) (3 g.) was refluxed for 2·5 hours with trimethylene glycol (20 c.c.), powdered potassium hydroxide (2·4 g.), and 90% hydrazine hydrate (2·4 c.c.). The condenser was removed and the boiling continued until the temperature of the liquid reached 195°. The condenser was then replaced and the refluxing continued for a further 2·5 hours. As some demethylation took place during the reduction, the mixture was cooled, diluted with sodium hydroxide solution, and treated at 60° with 3 successive portions (5 c.c. each) of methyl sulphate at intervals of 10 minutes. After 1 hours' heating on the water-bath, acidification and ether extraction gave an oil which was distilled under reduced pressure; δ-(3 : 4 : 5-*trimethoxyphenyl*)*valeric acid*, b. p. 210—220°/0·5 mm., crystallised from *cyclo*hexane in colourless plates, m. p. 70° (Found: C, 62·9; H, 7·5. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%), which were unaffected by 50% sulphuric acid.

2′ : 3′ : 4′-*Trimethoxybenz*cyclo*hepten*-3-*one* (XIV). Phosphoric oxide (8 g.) was added in small portions to a boiling solution of the above valeric acid (1 g.) in benzene (15 c.c.). After 2·5 hours the mixture was cooled, and the dark phosphorus-containing complex was decomposed with ice, rendered alkaline, extracted with ether, and dried. Removal of the ether yielded the *ketone* (XIV), which separated from *cyclo*hexane in colourless rhombs (0·6 g.), m. p. 102° (Found: C, 67·4; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). The 2 : 4-*dinitriphenylhydrazone* crystallised from ethyl acetate in orange elongated prisms, m. p. 176—177°.

γ-(3 : 4 : 5-*Trimethoxy*-2-*carboxyphenyl*)*butyric acid* (X). 2′ : 3′ : 4′-Trimethoxybenz*cyclo*hepten-3-one (XIV) (1 g.) was refluxed with selenium dioxide (0·6 g.; 25% excess) in dioxan (15 c.c.) for 6 hours. Selenium was collected from the cooled solution and the filtrate was warmed on the water-bath with sodium hydroxide (15 c.c. of 2N), hydrogen peroxide (10 c.c. of 20 vol.), and ethanol (15 c.c.). When evolution of oxygen ceased, more peroxide (10 c.c.) was added and the process repeated. The solution was cooled and a small amount of ketone (XIV) recovered by extraction with ether; the aqueous layer was acidified, and the acid (X), isolated with ether, was purified by solution in sodium hydrogen carbonate, recovery with ether, and crystallisation from acetone–ligroin. γ-(3 : 4 : 5-*Trimethoxy*-2-*carboxyphenyl*)-*butyric acid* was obtained in colourless prisms (0·25 g.), m. p. 146—147° (Found: C, 56·2; H, 5·9; equiv., 151. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·0%; equiv., 149).

Synthesis of γ-(2 : 3 : 4-*Trimethoxy*-6-*carboxyphenyl*)*butyric Acid* (IX).—γ-(2 : 3 : 4-*Trimethoxybenzoyl*)*butyric acid* (XI). Trimethyl pyrogallol (2 g.) and glutaric anhydride (2 g.) were added to a solution of aluminium chloride (5 g.) in nitrobenzene (20 c.c.) and the mixture left for 48 hours. The resultant viscous liquid was decomposed with ice and hydrochloric acid, steam distilled to remove nitrobenzene, and extracted with ether. Evaporation to a small bulk yielded a small amount of a γ-(*hydroxydimethoxybenzoyl*)*butyric acid*, which crystallised from aqueous alcohol and then from

benzene–ligroin, giving colourless needles, m. p. 174° (Found: C, 58·5; H, 6·5. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). The remaining oil, which solidified after 48 hours, was crystallised from *cyclo*hexane; colourless elongated prisms of *γ-(2 : 3 : 4-trimethoxybenzoyl)butyric acid*, m. p. 73—75° (Found: C, 60·0; H, 6·2. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%), were obtained.

δ-(2 : 3 : 4-Trimethoxyphenyl)valeric acid. The crude mixture of trimethoxybenzoylbutyric acid and the corresponding dimethyl ether was dissolved in toluene and reduced by Clemmensen's method for 18 hours. On concentration of the toluene layer a *δ-(hydroxydimethoxyphenyl)valeric acid* separated; it crystallised in stout prisms from benzene (charcoal), and in plates from water, m. p. 108—109° (Found: C, 61·3; H, 7·1. $C_{13}H_{18}O_6$ requires C, 61·4; H, 7·1%). This and the remaining oil were dissolved in excess of aqueous sodium hydroxide and methylated with methyl sulphate. The ether extract of the acidified solution yielded *δ-(2 : 3 : 4-trimethoxyphenyl)valeric acid*, b. p. 200—210°/0·15 mm., which crystallised from ligroin in prisms, m. p. 66—67° (Found: C, 62·6; H, 7·4. $C_{14}H_{20}O_6$ requires C, 62·7; H, 7·5%).

*1′ : 2′ : 3′-Trimethoxybenz*cyclo*hepten-3-one* (XII). Phosphoric oxide (10 g.) was added to a solution of δ-(2 : 3 : 4-trimethoxyphenyl)valeric acid (1 g.) in benzene (20 c.c.), and, after refluxing for 3 hours, the dark complex was decomposed with ice, rendered alkaline, and extracted with ether. The extract was washed with sodium hydroxide solution, dried, and distilled, yielding *1′ : 2′ : 3′-trimethoxybenz*cyclo*hepten-3-one* (0·5 g.), b. p. 170°/0·3 mm. (Found: C, 67·0; H, 7·6. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). The *2 : 4-dinitrophenylhydrazone* crystallised from aqueous acetic acid in orange-red plates, m. p. 179° (Found: C, 56·0; H, 5·3. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1%).

γ-(2 : 3 : 4-Trimethoxy-6-carboxyphenyl)butyric acid (IX). *1′ : 2′ : 3′*-Trimethoxybenz*cyclo*hepten-3-one (0·65 g.) was oxidised as described for the isomeric ketone (XIV) with selenium dioxide (0·4 g.) and then with hydrogen peroxide (15 c.c. of 20 vol. added in 2 portions). The resulting acidic oil was methylated with diazomethane in ethereal solution, and the dimethyl ester was distilled at 0·1 mm., and hydrolysed with aqueous sodium hydroxide; *γ-(2 : 3 : 4-trimethoxy-6-carboxyphenyl)butyric acid* crystallised from water in needles, m. p. 132° (Found: C, 56·4; H, 6·0. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·0%).

*4-Hydroxy-3-keto-2-carboxy*cyclo*heptatrienylacetic Acid* (XV; R = H).—A steady stream of carbon dioxide-free air was drawn through a solution of purpurogallin (2 g.) in 5% potassium hydroxide (150 c.c.) for 20 hours. The solution was acidified with dilute sulphuric acid, the precipitated humic acid was collected, and the filtrate was extracted continuously with ether for 20 hours. The extract was decanted from tar, clarified with charcoal, dried, and evaporated. The residual amber oil gradually deposited a crystalline solid (0·11 g.) which was freed from oily impurities with a little ether and recrystallised from ligroin containing a small amount of acetone; colourless prisms, m. p. 182° (decomp.) (Found: C, 53·7; H, 3·6; equiv., 76. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%; equiv., 75), were obtained which dissolved in aqueous sodium hydrogen carbonate giving a bright yellow solution and gave a deep red ferric test. The *methyl 3-keto-2-carbomethoxy-4-methoxy*cyclo*heptatrienylacetate* (XV; R = Me), prepared by the action of diazomethane in ether–acetone solution, crystallised from benzene in colourless needles, m. p. 110° (Found: C, 58·9; H, 5·6. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3%).

*2-Hydroxy-6-methyl*cyclo*heptatrienone* (XVI), prepared by decarboxylation of the acid (XV; R = H) by heating at the melting point, was purified by sublimation; colourless prisms, m. p. 77° (Found: C, 70·2; H, 6·2; equiv., 136. $C_8H_8O_2$ requires C, 70·5; H, 5·9%; equiv., 136), which dissolved with effervescence in aqueous sodium hydrogen carbonate and gave a green ferric test, were obtained.

Our thanks are due to Mr. R. C. Brian, B.Sc., for assistance with the preliminary experiments in 1943, to the Department of Scientific and Industrial Research for a maintenance grant (to B. P. M.), to the University of Sheffield for the award of a Henry Ellison Fellowship (to P. L. P.), and to Imperial Chemical Industries Ltd. for a grant which has defrayed some of the expenses of this investigation.

THE UNIVERSITY, SHEFFIELD. [*Received, July 24th*, 1947.]

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208. *Electrolytic Dissociation Processes. Part V. The Solvolytic Ionisation of Molecular Iodine.*

By FRED FAIRBROTHER.

The polarisation or ionisation of an iodine molecule by co-ordinate bond formation with a "basic" solvent molecule is discussed. Measurements have been made of the dielectric constants and densities of solutions of iodine in a number of solvents of zero or low polarity. Solvents with basic or electron-donor character give red or brown solutions with an enhanced dielectric polarisation: this group includes aromatic and ethylenic hydrocarbons, whose electron-donor character is attributed to the π electrons.

THE fact that solutions of iodine in non-aqueous solvents vary, according to the solvent, both in colour and in chemical properties has been known for a very long time: and although it has become generally recognised that the essential difference between a purple solution and a brown one lies in the presence in the latter of loose solvent–solute complexes, usually termed solvates, the structure of these complexes and the circumstances which determine their formation remain obscure.

The formation of an iodine–solvent complex is clearly not a matter of simple electrostatic

solvation by polar solvent molecules, for it has little to do with the dielectric constant of the solvent, but rather does it appear to be a consequence, on the one hand, of the amphoteric nature of iodine and the electronic structure of the positive univalent iodine cation, and on the other hand, of the electron-donor characteristics of the solvent molecules.

It is well established that iodine can exist, not only as the more familiar negative iodide ion, but also as a univalent cation (cf. Gmelin, " Handb. d. anorg. Chem.", 8 Aufl., Nr. 8, 454 ff., Berlin, 1933). The first indication of the positive nature of iodine was given by Faraday (*Phil. Trans.*, 1833, 506), who showed that its liquid monochloride would conduct electricity and that iodide was liberated at the negative pole. Electrochemical investigations by later workers have confirmed completely the presence of the iodine cation in ICI, either in the fused state or when dissolved in polar inorganic solvent. Even dissolution of ICI in a non-polar solvent such as carbon tetrachloride or *cyclo*hexane will bring about an increase in the ionic character of the molecule (Fairbrother, *J.*, 1936, 847).

Iodide hydroxide, IOH, usually called "hypoiodous acid", is rather more basic than acidic: $K_a = [H^+][IO^-]/[IOH] = 2—3 \times 10^{-11}$ at 25° (Furth, *Z. Elektrochem.*, 1922, **28**, 57) and $K_b = [I^+][OH^-]/[IOH] = 3{\cdot}2 \times 10^{-10}$ at 25° (Murray, *J.*, 1925, **127**, 885). Cofman (*J.*, 1919, **115**, 1040) showed conclusively that this hydroxide is the active substance in the iodination of phenols, and clearly recognised that its properties showed it to be the hydroxide of a positive iodine ion.

Further, Carlsohn (*Angew. Chem.*, **45**, 580; 1933, **46**, 747), by treating the silver or mercurous salt of the appropriate acid with the calculated amount of iodine and a slight excess of pyridine or of one of its derivatives dissolved in some non-aqueous solvent, has prepared a whole series of crystalline oxy-acid salts of iodine; half the iodine in this reaction is precipitated as an insoluble iodide and the remainder forms a stable salt of a univalent iodine cation. Even from a solution of iodine in pyridine alone, an unstable compound PyI_2 may be precipitated by the addition of water (Waentig, *Z. physikal. Chem.*, 1909, **68**, 513).

It would appear that the formation of these compounds is a result of the strongly donor character of the basic nitrogen lone-pair of electrons, which stabilise the positive iodine ion, and although similar compounds do not appear to have prepared from other brown solutions of iodine, nevertheless it is not unreasonable to suppose that—parallel with the shift towards the violet of the visible absorption band—some polarisation may occur also in other basic solvents.

The mechanism by which such a process can occur may be understood by a consideration of the electronic structures of the iodine molecule and the iodine ions.

The wave function representing the single valence bond in a homonuclear diatomic molecule A–A can be written:

$$\Psi = a\psi_{A:A} + b\psi_{A^+A^-} + b\psi_{A^-A^+}$$

(Pauling, " The Nature of the Chemical Bond ", Cornell, 1940, p. 47), in which the squares of the coefficients a and b represent the contributions respectively of the purely covalent and of the ionic structures in which both valency electrons are associated with the same nucleus.

In the hydrogen molecule it is estimated that each of the two ionic structures H^+H^-, H^-H^+ makes a contribution of about 2% to the normal state of the molecule. There is, however, not much evidence as to the amount of ionic character of other single bonds between like atoms (Pauling, *op. cit.*), but although considerations of the energy required to convert, for instance, an extreme covalent Cl–Cl pair into an ion-pair might make it appear that the ionic terms make very little contribution to the normal state of the chlorine, yet other considerations suggest that in some cases, especially in the case of iodine, the ionic contribution may be quite significant. Energy calculations show that it requires only about 15 kcals./mol. more to convert a gaseous iodine molecule into an ion-pair than to form an ion-pair from a gaseous ICl molecule, which undergoes solvolytic ionisation with relative ease.

Moreover, there is evidence to show that the valency electrons in the iodine molecule are relatively easily polarised, since the combination of two neutral iodine atoms to form a molecule is accompanied both by development of visible colour and by a marked increase in refractivity: atomic iodine is colourless, and only absorbs radiation of a shorter wave-length than 2300 A. (v. Angerer and Joos, *Ann. Physik*, 1924, **74**, 756), whilst the enhanced polarisability of the electrons in molecular iodine is shown by the work of Braun and Hölemann (*Z. physikal. Chem.*, 1936, *B*, **34**, 357). These authors made careful interferometer measurements of the refractivity of gaseous iodine from 150° to 1030° for the red hydrogen line ($\lambda = 6563$ A.) and found that the atomic refractivity was $13{\cdot}4 \pm 0{\cdot}2$ c.c. whilst the molar refractivity of the undissociated diatomic molecule was $32{\cdot}2 \pm 0{\cdot}2$ c.c. These measurements were necessarily carried out still in the

region of absorption, for the bands extend far into the red, with the maximum absorption in the green (*ca.* 5000 A.), but the earlier work of Cuthbertson (*Phil. Trans.*, 1914, *A*, **213**, 1) on the refractivities of the halogens at a number of wave-lengths indicates that this high refractivity is not simply a matter of anomalous dispersion, for there appear to be no sudden changes of the refractivities of the halogens in passing through the absorption bands.

The refractivity of gaseous atomic iodine is closely similar to the atomic refractivity of iodine in an organic iodide (13·76 c.c. for H_α; Eisenlohr, *Z. physikal. Chem.*, 1911, **75**, 585), so that the refractivity of the iodine molecule is some 20% greater than the sum of the refractivities of the separated atoms or of two single electron-pair-bonded iodine atoms.

Two separate neutral iodine atoms together contain two 5*p* orbitals, each containing a single electron. When the two atoms come together to form a molecule, these two electrons may occupy a molecular orbital composed of the two 5*p* atomic orbitals to form a normal covalent bond or, somewhat less easily since the process is endothermic by nearly 2·5 e.v., to form an ion pair in which the two valency electrons occupy, with paired spins, a single 5*p* orbital leaving the other vacant, *i.e.*, I^+I^- or I^-I^+. The actual iodine molecule is a hybrid of these three structures.

Further, a molecule A, of a second substance, which possesses a sufficiently mobile pair of electrons, *e.g.*, a lone-pair, can form a co-ordinate bond with the atom which has a vacant 5*p* orbital, and thus its approach to the iodine molecule would stabilise one of the ionic structures. If the 5*p* orbital of the acceptor atom is wholly utilised in forming the co-ordinate bond, it will no longer be available for the iodine valency electrons, which will then pass to the 5*p* orbital of the further atom and the structure become wholly ionic : $A : I^+.I^-$. On the other hand, if the wave function of the donor electrons is such as to overlap the 5*p* orbital in question only to a limited extent, a new composite molecule will be formed in which the iodine is polarised by attachment to the donor molecule. This in terms of valence-bond theory may be described by saying that the relative contribution of one of the ionic forms had been increased. When iodine is dissolved in a medium which is both highly basic and polar, some actual electrolytic dissociation may occur, the energy necessary for the ionisation of the neutral molecule being supplied by the energy of co-ordinate bond formation and of solvation of the resulting ions.

It is suggested that the form of the iodine "acceptor" orbital is labile and that the iodine molecule adjusts itself to accommodate the donor electrons. Thus the degree of polarisation of the iodine and the strength of the solvent–solute bond will depend on the donor or "basic" (cf. Lewis, "Valence and the Structure of Atoms and Molecules", New York, 1923, p. 142) character of the solvent. This in turn would account for the experimental observation that the visible absorption band is most displaced towards the violet (*i.e.*, the solution is browner) in basic solvents and hardly displaced at all in highly polar but non-basic solvents like the nitro-paraffins. Iodine forms an electrically conducting solution in dry pyridine (Audrieth and Birr, *J. Amer. Chem. Soc.*, 1933, **55**, 668) but a non-conducting solution in nitrobenzene unless a trace of moisture is present (Bruner and Galecki, *Z. physikal. Chem.*, 1913, **84**, 513). It seems very improbable that the solutions of iodine are of two distinct types only—purple and brown—as suggested by Lachman (*J. Amer. Chem. Soc.*, 1903, **25**, 50), rather that a more or less continuous series exists according to the basicity of the solvent. That the solvent–iodine bond is often of a weak nature is shown by the sensitivity of the colour of many solutions to a change of temperature, the colour becoming more purple or less brown with rise of temperature, and *vice versa*.

The ionisation and dissociation of iodine into *separate* positive and negative ions has been postulated by several authors to account for experimental observations. Lewis (*op. cit.*, p. 83) pointed out that the octet theory offered an explanation of this ionisation into an anion with a complete octet and a cation with six valency electrons which would account for the electrical conductivity of molten iodine; and Winther (*Z. physikal. Chem.*, 1929, *B*, **3**, 299) found it necessary to assume the existence of I^+ in aqueous solutions in order to account quantitatively for the distribution of iodine between carbon tetrachloride and water or aqueous potassium iodide or hydrochloric acid.

It has now been demonstrated, by means of dielectric-polarisation measurements, that when iodine is dissolved in a medium of zero or low polarity but possessing bonds or groups with electron-donor character, there results a polarisation of the iodine, which is accompanied by the formation of a red or brown solution. In *cyclo*hexane, which has no electron-donor character, the dipole moment is zero and the colour is purple.

The interpretation of measurements of dielectric polarisation in polar basic solvents, which also form red or brown solutions, is more difficult, and indeed such measurements may be impracticable on account of the electrolytic dissociation of the ionised iodine. In this connection may

be cited the work of Higasi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1934, **24**, 57), who found the moment of iodine in diethyl ether to be 0·7 D. but stated that the results were less reliable than for other solutes in ether because "the ether solution of iodine is found to be a little conductive".

Several more or less tentative suggestions have been put forward (*e.g.*, Williams, *Physikal. Z.*, 1929, **29**, 174; Dewar, *J.*, 1946, 406) inferring some degree of ionisation of iodine in benzene solution on the basis of its abnormal colour and dipole moment. The available evidence, however, regarding the magnitude or even the existence of such a dipole moment in benzene and other non-polar solvents is extremely unsatisfactory and conflicting.

Williams and Allgeier (*J. Amer. Chem. Soc.*, 1927, **49**, 246) measured the polarisation of iodine in benzene at 25° over the range of its solubility and gave the molar polarisation as 60·2 c.c. at each concentration. Estimating the electronic polarisation as 20 c.c., they ascribed to iodine a moment of 1·4 D. In a later paper, Williams (*Physikal. Z.*, 1928, **29**, 174) took the electronic polarisation as 28 c.c., giving (on the former polarisation figures) a moment of 1·2 D.; the same moment is given for carbon disulphide solutions on the basis of polarisation data obtained by Williams and Ogg (*J. Amer. Chem. Soc.*, 1928, **50**, 94).

The next investigation was by Müller and Sack (*Physikal. Z.*, 1930, **31**, 815) who, without giving any experimental figures, state that the moment in hexane and *cyclo*hexane is zero and in benzene 1·0 D. In a later paper (*ibid.*, 1933, **34**, 689) Müller gives the total polarisation figures—again without any details of individual measurements—as 20 c.c. in hexane, 20 c.c. in *cyclo*hexane, 39 c.c. in carbon tetrachloride, 50 c.c. in benzene, 32 c.c. in carbon disulphide, with a total molar refraction of 28·5 c.c. It may be observed that here the total polarisation in hexane and *cyclo*hexane is given as less than the refractivity, whilst the values in benzene and in carbon disulphide differ widely from those quoted by Williams.

Finally, from a study of the dielectric polarisation of iodine in benzene, in five concentrations measured over a temperature range of 50° (from 15° to 65°), Kaftanow Wassiliew, and Syrkin (*Acta Physicochim. U.R.S.S.*, 1937, **7**, 75) conclude that the dipole moment of iodine in benzene is zero and that their results "refute the hypotheses which were formerly made to the effect that the dipole moment is due to some kind of associated compounds".

A close examination of their experimental results, however, reveals a fallacy in the argument. They obtain an average molar polarisation of the iodine of 41·12 c.c., which does not differ greatly from the figure (38·5 c.c.) obtained in the present work. They argue that the moment calculated from this figure in the usual manner, assuming an electronic polarisation of 32 c.c., which would be 0·66 D., would mean in turn that the molar polarisation ought to diminish by 1·4 c.c. over the temperature range of measurement, and, which they state, they do not observe. This apparent temperature-independent polarisation, however, is obtained by averaging the polarisation *at each temperature* over all the concentrations. A rearrangement of the data to show the effect of change of temperature on polarisation *in each solution* reveals that the two most concentrated solutions, which are the most significant, actually do show a decrease of polarisation, of 1·16 and 2·24 c.c. respectively, and it is only the less significant results in the weaker solutions, where the effect of experimental error is greatly magnified, which give the impression, by this method of averaging, of a temperature-independent polarisation.

In Table I are given the results of measurements of the dielectric polarisation of iodine in a number of solvents of zero or low polarity and of varying "basic" character; f_2 is the mol.-fraction of iodine, ε and d respectively the dielectric constant and density of the solution, and P_2 the molar polarisation of the iodine calculated in the usual manner from the difference between the total polarisation and the fractional polarisation of the solvent.

The low solubility and low polarisation of iodine in *cyclo*hexane, coupled with the maximum attainable precision of measurement of ε and d, impose an uncertainty of about $\pm$ 1 c.c. in the value of P_2 in this solvent. It is noteworthy, however, that this value (31 c.c.), which corresponds to the refractivity at zero frequency, agrees much more closely with the refractivity of gaseous iodine than with the lower value appropriate to electron-pair-bonded atoms.

Measurements in *cyclo*hexene were made difficult by the photosensitivity of the solutions which rapidly faded even in diffused daylight. The solutions were therefore made up in black-painted flasks and exposed to light as little as possible. A further complication in the case of *cyclo*hexene is the slow spontaneous change undergone by the solvent itself, even under conditions of complete exclusion of moisture, though not of dry air. This results in a slow increase of both ε and d and necessitates blank determinations of the solvent polarisation each day.

In Table II are calculated the apparent moments of iodine in the several solvents. A large number of refractivity measurements were made on the solutions. The results were grouped

TABLE I.

Iodine in cyclo*hexane.*				*Iodine in benzene.*			
f_2.	ϵ.	d.	P_2 (c.c.).	f_2.	ϵ.	d.	P_2 (c.c.).
0·0000	2·0140	0·7732	—	0·0000	2·2727	0·8732	—
0·001931	2·0151	0·7767	30·0	0·004723	2·2790	0·8839	37·1
0·002938	2·0161	0·7786	32·3	0·007030	2·2823	0·8891	37·8
0·003540	2·0164	0·7798	30·8	0·008982	2·2853	0·8934	38·3
0·003780	2·0164	0·7802	30·7	0·01279	2·2913	0·9018	39·9
		Average	31 c.c.	0·01919	2·3006	0·9162	39·7
						Average	38·5 c.c.
Iodine in p-*xylene.*				*Iodine in* cyclo*hexene.*			
0·0000	2·2596	0·8569	—	0·0000	2·2200	0·8062	—
0·005201	2·2666	0·8654	46·3	0·007355	2·2381	0·8219	55·3
0·006610	2·2689	0·8677	47·3	0·01061	2·2470	0·8290	56·0
0·01442	2·2798	0·8803	47·4	0·0000	2·2236	0·8064	—
0·01879	2·2861	0·8878	46·6	0·01871	2·2716	0·8466	56·0
0·01985	2·2871	0·8893	46·6	0·0000	2·2244	0·8065	—
		Average	47 c.c.	0·007662	2·2435	0·8230	54·6
				0·01431	2·2624	0·8372	57·7
						Average	56 c.c.
Iodine in 1 : 4-*dioxan.*				*Iodine in diisobutylene.*			
0·0000	2·2118	1·0277	—	0·0000	2·0908	0·7123	—
0·005368	2·2294	1·0395	65·8	0·007133	2·1063	0·7221	75·6
0·007975	2·2385	1·0452	66·7	0·009464	2·1114	0·7253	75·4
0·008049	2·2379	1·0452	65·7	0·01047	2·1136	0·7268	74·9
0·01097	2·2492	1·0518	67·4	0·01263	2·1182	0·7296	75·5
0·01350	2·2571	1·0572	66·8	0·01723	2·1287	0·7361	75·4
		Average	66·5 c.c.			Average	75 c.c.

around an average value of about 29 c.c. for H_α (6563 A.), but owing to the opacity of the concentrated solutions, on the one hand, and the uncertainty which necessarily accompanies measurements on dilute solutions, on the other, this figure is probably not better than $\pm$ 1 c.c. Since, however, the total dielectric polarisation in *cyclo*hexane, which has no basic or donor properties, and in which the iodine dissolves to give a purple solution, presumably of symmetrical dipole-free iodine molecules, is 31 $\pm$ 1 c.c., this figure has been taken for P_{e+a} in the calculation of the apparent dipole moment. An error of $\pm$ 1 c.c. would not affect the moments as given, which are expressed only to the first decimal place.

TABLE II.

Solvent.	Colour.	P_2 (c.c.).	P_e (c.c.).	μ (D).
*cyclo*Hexane	Purple	31	0	0·0
Benzene	Reddish purple	38·5	7·5	0·6
p-Xylene	Red	47	16	0·9
*cyclo*Hexene	Red-brown	56	25	1·1
1 : 4-Dioxan	Brown	66·5	35·5	1·3
Di*iso*butylene	Red-brown	75	44	1·5

It should be emphasised that these are only the apparent moments, since the polarisation includes also the effect of electronic shifts within the donor molecule. A quantitative correlation between the colour of the solution and the magnitude of the apparent dipole moment is therefore not to be expected. For instance, dilute solutions in 1 : 4-dioxan appear browner than solutions in *cyclo*hexene or in di*iso*butylene. The evidence for the formation of polar complexes in the red and the brown solutions is, however, unmistakable.

Of especial interest is the evidence of the bonding power of aromatic and ethylenic bonds. In these compounds the donor electrons are probably the π electrons, as suggested by Dewar (*loc. cit.*) for the case of benzene. It may be noted that a greater total electronic shift occurs in the case of ethylenic compounds, where the π electrons are less firmly bound than in the benzene ring.

EXPERIMENTAL

Materials.—cyclo*Hexane.* A commercial product was shaken with concentrated sulphuric acid, to which about 10% of "10% oleum" had been added, for more than 12 hours: very little browning occurred. It was then washed, kept over potassium hydroxide pellets for a week, then set aside for several weeks in contact with phosphoric oxide, and fractionated through an efficient column in a stream of nitrogen, dried by passage through a coil immersed in liquid air; b. p. 81·1° $\pm$ 0·1°/757 mm.

Benzene. " AnalaR " Benzene was fractionally frozen three times to remove homologues, kept for several months over phosphoric oxide, and fractionated in dry nitrogen as above; b. p. 80·1° ± 0·1°/762 mm.

p-*Xylene.* A commercially pure product was dried by long contact with phosphoric oxide, and fractionated in dry nitrogen; b. p. 137·3° ± 0·1°/748 mm.

cyclo*Hexene.* A commercial product, after a preliminary fractionation, was refluxed for 12 hours over sodium, and fractionated from fresh sodium in a stream of dry nitrogen; b. p. 82·2° ± 0·2°/758 mm.

1 : 4-*Dioxan.* A commercial product was refluxed with ~ 10% of its volume of N-hydrochloric acid in a stream of nitrogen to decompose the acetal and remove the acetaldehyde (cf. Eigenberger, *J. pr. Chem.*, 1931, **130**, 75). It was then treated with potassium hydroxide pellets until no further water separated on standing and the pellets did not adhere, refluxed over sodium for two hours and fractionated in a stream of nitrogen, and finally refluxed for 6 hours over potassium and again fractionated from potassium in a stream of dry nitrogen; b. p. 100·3° ± 0·1°/750 mm.

Diisobutylene. A sample kindly presented by Messrs. Imperial Chemical Industries Ltd. (Billingham) and consisting originally of about 80% of 2 : 2 : 4-trimethylpent-4-ene and about 20% of the Δ^3-isomer was given an initial drying over anhydrous sodium sulphate, refluxed over sodium for two hours, and over potassium for six hours, and finally distilled from potassium in a stream of dry nitrogen; b. p. 101·5° ± 0·1°/748 mm.

Iodine. " AnalaR " Iodine was resublimed in a current of dry nitrogen.

All solvents were stored over anhydrous magnesium perchlorate in vessels of the form previously described (Part IV, *J.*, 1945, 503).

Measurements.—Dielectric constants and densities were measured as previously described (Part IV, *loc. cit.*). Refractive indices were measured by a Pulfrich refractometer in which the usual silvered immersion heater was replaced by a glass heater (Fairbrother, *J.*, 1932, 43) to prevent chemical action by the iodine solutions.

I am indebted to Messrs. Imperial Chemical Industries Ltd. for a grant for the purchase of apparatus.

THE UNIVERSITY OF MANCHESTER. [*Received, July 22nd,* 1947.]

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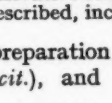
209. *Studies in the Azole Series. Part IV. The Preparation of Some Thiazolones.*

By A. H. COOK, G. HARRIS, SIR IAN HEILBRON, and G. SHAW.

Several α-amino-acids have been converted into *N*-dithiocarbamic esters which have been dehydrated to derivatives of 2-mercaptothiazolone (I; R = H) (Part III, this vol., p. 201), though a comparable *N*-monothiocarbamic ester could not be converted into the corresponding derivative of 2-mercapto-oxazolone. Some reactions of 2-benzylthiothiazolone in particular are described, including attempts to elaborate an analogue of penicillin.

THE preparation and properties of 2-mercaptothiazolone (I; R = H) were described in Part III (*loc. cit.*), and the present paper is concerned with some indirect derivatives of this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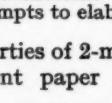
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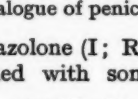
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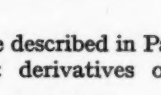
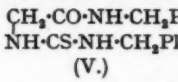

(IV.)

compound where R = a hydrocarbon residue. A search of the literature revealed very few compounds of this kind, and even dithiocarbamic esters of α-amino-acids, which may be expected to yield such thiazolones by dehydration, have rarely been studied. Thus, esters of *N*-dithiocarboxyglycine (*e.g.*, II) have been described (Körner, *Ber.*, 1908, **41**, 1901) and one compound of this kind has been converted into the thiazolone derivative (III) (Fourneau and Vila, *Bull. Soc. chim.*, 1911, **9**, 985).

We have now found that the alkali salt of the dithiocarbamic acid resulting from glycine and carbon disulphide readily affords N-*dithiocarbobenzyloxyglycine* (IV) in excellent yield on treatment with benzyl chloride. On treating (IV) with phosphorus tribromide in ether a highly crystalline *hydrobromide* was formed which tended to lose hydrogen bromide in air but there was no doubt from its reactions that it was the salt of 2-benzylthiothiazolone (I; R = CH_2Ph). With diazomethane (cf. Karrer and Widmer, *Helv. Chim. Acta*, 1925, **8**, 203; Karrer and Hussmann, *ibid.*, 1941, **24**, 645) it afforded an unidentified crystalline product which was not the expected free base. When the hydrobromide was shaken with alkali it reverted to compound (IV). With benzylamine in boiling ether it gave benzylamine hydrobromide together with the *bisbenzylamide* (V). On the other hand, the free thiazolone (I; R = CH_2Ph) was obtained by treating the above hydrobromide with aqueous sodium acetate. This compound reacted with benzylamine in the cold to give the *monobenzylamide* (VI).

2-Benzylthiothiazol-5-one (I; R = CH_2Ph) was of interest in relation to penicillin-II (benzylpenicillin; *Nature*, 1945, **156**, 766; *Science*, 1945, **102**, 622) which, when the present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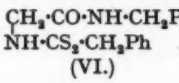
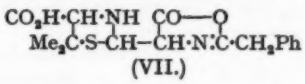
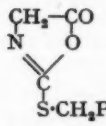
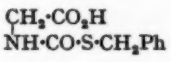
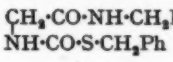

(VI.)


(VII.)

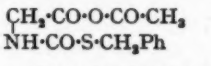
work was carried out, was thought might be (VII). It appeared desirable, therefore, not only to attempt to elaborate (I; R = CH_2Ph) into an analogue of (VII) but also to investigate the corresponding oxazolone (VIII).

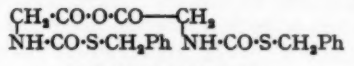

(VIII.)

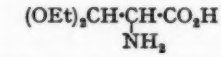

(IX.)

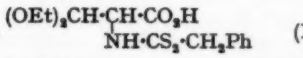

(X.)

A convenient approach appeared to be *via* the *monothio-ester* (IX) which was obtained in poor yield by oxidising the corresponding dithio-ester with hydrogen peroxide in cold alkali. Attempts to improve this preparation by the interaction of glycine and benzyl chloromonothioformate, Cl·CO·S·CH_2Ph, were unsuccessful. The ester (IX) gave with acetic anhydride in the steam-bath a crystalline compound, $C_{12}H_{13}O_4NS$, which, although it reacted with benzylamine giving the expected *benzylamide* (X), was almost certainly not a derivative of the oxazolone (VIII) but the mixed *anhydride* (XI). When the latter or the ester (IX) was boiled

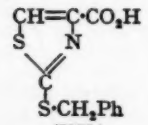
(XI.) 

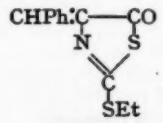

(XII.)

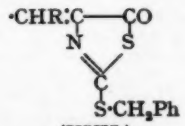
(XIII.) 

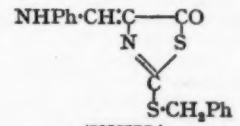

(XIV.)

with acetic anhydride a new crystalline compound, $C_{20}H_{20}O_5N_2S_2$, arose. As the latter gave the same benzylamide (X), it was obviously the *anhydride* (XII). As no better success attended attempts to dehydrate the ester (IX) by means of phosphorus tribromide, attention was redirected to the 2-benzylthiothiazolone series. In the first place attempts were made to apply the relevant reactions to ββ-diethoxyalanine (XIII), treatment of which with carbon disulphide followed by benzyl chloride gave ββ-*diethoxy*-N-*dithiocarbobenzyloxyalanine* (XIV). In attempting to condense the latter compound with ββ-dimethylcysteine (penicillamine) a crystalline acid was formed which, however, was not the anticipated penicillin analogue but gave analytical data corresponding to $C_{11}H_9O_2NS_2$. As the same compound was obtained in the absence of penicillamine, it can only be 2-*benzylthio*-4-*carboxythiazole* (XV) formed by cyclisation. The first indication of a reactive methylene group in a thiazolone (I) was the formation of 2-*ethylthio*-4-*benzylidenethiazolone* (XVI) from the ester (II), benzaldehyde, and acetic anhydride. 2-Ethylthiothiazolone itself (I; R = Et) was formed on treating the ester (II) with acetic anhydride or with phosphorus tribromide, as shown by reaction of the product with benzylamine to give the dibenzylamide (V). Continued work with the ethylthio-derivatives was complicated by the great reactivity of the SEt grouping, attempts to oxidise the ester (II) to the analogue of (IX), for example, failing because of hydrolysis.


(XV.)


(XVI.)


(XVII.)


(XVIII.)

In view of the observed reactivity of the methylene group it was not surprising to find that interaction of 2-benzylthiothiazolone with ethyl orthoformate and acetic anhydride afforded 2-*benzylthio*-4-*ethoxymethylenethiazolone* (XVII; R = OEt), identical with the compound obtained from the derivative (XIV) and acetic anhydride. The compound (XVII; R = OEt) was remarkably reactive. It condensed readily with aniline to give 2-*benzylthio*-4-*anilinomethylenethiazolone* (XVIII), and cold aqueous sodium hydroxide converted it into the corresponding 2-*benzylthio*-4-*hydroxymethylenethiazolone* (XVII; R = OH). Unexpected, however, was the reaction of (XVII; R = OEt) with sulphanilamide, wherein the product was not the expected sulphanilamidomethylenethiazolone for it contained an additional molecule of ethanol.

Acetylsulphanilamide was unaffected under similar conditions, so reaction obviously took place on the nuclear amino-group. As it was shown that ethanol was not introduced during reaction, this product is regarded as the *acyl* compound (XIX). It had no outstanding antibacterial activity.

(XIX.) $\begin{matrix} OEt\cdot CH{:}C\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH_2(p) \\ | \\ NH\cdot CS\cdot S\cdot CH_2Ph \end{matrix}$ $\qquad$ $\begin{matrix} CH(CO_2Et)_2 \\ | \\ NH\cdot CS_2\cdot CH_2Ph \end{matrix}$ (XX.)

Most of the reactions so far described were paralleled in other series to establish their general nature and for more specific reasons. Thus the interaction of ethyl aminomalonate, carbon disulphide, alkali, and benzyl chloride gave the *benzyl* N-*dithio*-ester (XX), while interaction of *N*-dithiocarbobenzyloxyglycine and benzaldehyde in acetic anhydride gave 2-*benzylthio*-4-*benzylidenethiazolone* (XVII; R = Ph). Again, *N*-dithiocarbethoxyglycine and acetic anhydride afforded 2-ethylthiothiazolone whereas in presence of ethyl orthoformate it gave the corresponding 4-*ethoxymethylene* compound. Similarly, glycine, carbon disulphide, alkali and ethyl chloroformate gave N-*dithiocarbocarbethoxyglycine* (XXI), which with ethyl orthoformate and acetic anhydride afforded the corresponding 2-*carbethoxythio*-4-*ethoxymethylenethiazolone*.

(XXI.) $\begin{matrix} CH_2\cdot CO_2H \\ | \\ NH\cdot CS_2\cdot CO_2Et \end{matrix}$ $\qquad$ $\begin{matrix} CO_2Me\cdot CH\text{—}NH\ CO\text{—}S \\ | \quad\quad | \quad\quad | \\ Me_2C\cdot SH\ CH{=}C\text{–}N{=}C\cdot SR \end{matrix}$ (XXII.)

When (XVII; R = OH) and penicillamine methyl ester were brought together in cold ethanol the solution soon ceased to give the ferric chloride and nitroprusside colour reactions of the thiol ester. Although the crystalline product, $C_{17}H_{20}O_3N_2S_2$, gave no catalytic polarographic step, yet anodic oxidation in the polarograph left no doubt that it still contained a thiol grouping. It was therefore formulated as the *penicillenate* analogue (XXII; R = CH_2Ph), a constitution which is confirmed by the similarity of the light absorption of the compound to that of compound (XVII; R = OEt), and by its hydrolysis to the hydroxymethylene derivative (XVII; R = OH) by aqueous sodium hydroxide. The "penicillenate" (XXII) had no antibacterial activity and attempts to complete the thiazolidine ring were unsuccessful. A similar *compound* (XXII; R = Et) was obtained from the appropriate ethoxymethylene compound. Finally, penicillamine itself and the ethoxymethylene compound (XVII; R = OEt) gave the *acid* corresponding to (XXII; **R** = CH_2Ph), which was likewise devoid of biological activity.

Experimental.

Dithiocarbobenzyloxyglycine and its Reactions.—Glycine (15 g.) in cold water (50 c.c.) containing potassium hydroxide (23·3 g.) was shaken with carbon disulphide (15·2 g.) until a homogeneous solution was obtained (*ca.* 1½ hours), whereupon shaking was resumed (further 1½ hours) with benzyl chloride (25 g.); the white precipitate which soon appeared on adding benzyl chloride eventually redissolved and the clear yellowish solution was acidified to give the crude ester (45 g., m. p. 145—150°). N-*Dithiocarbobenzyloxyglycine* (IV) was purified by solution in aqueous sodium hydrogen carbonate and reprecipitation with acid, and by crystallisation from ether–light petroleum, separating in colourless needles, m. p. 164° (Found: C, 50·2; H, 4·7; N, 5·75; equiv., by titration, 242. $C_{10}H_{11}O_2NS_2$ requires C, 49·8; H, 4·6; N, 5·8%; equiv., 241). The preceding compound (1 g.) in dioxan (10 c.c.) and ether (30 c.c.) was treated with phosphorus tribromide (1·5 g.). After standing overnight the clusters of needles (1·2 g.) were collected and washed with ether; the compound, believed to be 2-*benzylthiothiazolone hydrobromide*, was free from phosphorus but could not be crystallised without decomposition; it had m. p. 96—97° (Found: C, 41·65; H, 3·95; N, 4·9. $C_{10}H_{10}O_2NSBr$ requires C, 41·65; H, 3·5; N, 4·85. $C_{10}H_{10}ONS_2Br$ requires C, 39·4; H, 3·3; N, 4·6%). The hydrobromide (0·24 g.) was triturated with an excess of ethereal diazomethane until solution was complete, and the crystalline *product* obtained on concentration (50 mg.) was recrystallised from chloroform–light petroleum, forming needles, m. p. 144—145° (Found: C, 50·5; H, 4·8; N, 13·3%). The hydrobromide (0·2 g.) was shaken with 1N-potassium hydroxide and the filtrate acidified. *N*-Dithiocarbobenzyloxyglycine was precipitated and identified with authentic material. When the hydrobromide (0·5 g.), benzylamine (1 c.c.), and ether (2 c.c.) were warmed, and the solution added to 2N-hydrochloric acid (25 c.c.) at 0°, a crystalline precipitate was obtained. It was purified by washing with aqueous sodium hydrogen carbonate, water, and ether, and crystallised from ethyl acetate–light petroleum; N-*benzylthiocarbamidoglycine benzylamide* (V) separated in rosettes of needles, m. p. 145—146° (Found: C, 64·85; H, 6·15; N, 13·0. $C_{17}H_{19}ON_3S$ requires C, 65·15; H, 6·1; N, 13·4%). The thiazolone hydrobromide (2·0 g.) was shaken with ether (30 c.c.) and aqueous 10% sodium acetate (50 c.c.). On drying and evaporating the ether layer, 2-*benzylthiothiazolone* (I; R = CH_2Ph) was recovered. It separated from light petroleum in long laths, m. p. 45° (Found: C, 53·9; H, 4·1; N, 6·5. $C_{10}H_9ONS_2$ requires C, 53·8; H, 4·1; N, 6·3%) (yield, 1·0 g.), and was insoluble in aqueous sodium hydrogen carbonate. The thiazolone (0·1 g.) was kept for a few minutes with benzylamine (0·5 g.), and 2N-hydrochloric acid added in excess. N-*Dithiocarbobenzyloxyglycine benzylamide* (VI) (0·13 g.) was collected and recrystallised from ethyl acetate, separating in needles, m. p. 163° (Found: C, 62·1; H, 5·5; N, 8·8. $C_{17}H_{18}ON_2S_2$ requires C, 61·8; H, 5·5; N, 8·5%).

Monothiocarbobenzyloxyglycine and its Reactions.—*N*-Dithiocarbobenzyloxyglycine (5·0 g.) was treated with 1N-potassium hydroxide (62·5 c.c.) and 3% hydrogen peroxide, and the new acid precipitated by

acidification (yield, 1·1 g., m. p. 146—147°). N-*Monothiocarbobenzyloxyglycine* (IX) separated from water in needles, m. p. 146—147° (Found: C, 53·2; H, 4·7; $C_{10}H_{11}O_3NS$ requires C, 53·3; H, 4·9%). The preceding acid (0·2 g.) was heated on the steam-bath for 5 mins. with acetic anhydride (3 c.c.) and excess of reagent removed in a vacuum; the residue crystallised. A little ether-insoluble material was removed and the ether-soluble product crystallised from ethyl acetate containing a little light petroleum; the mixed *anhydride* (XI) separated in colourless needles, m. p. 79° (Found: C, 54·0, 54·15; H, 4·8, 5·2; N, 5·3, 5·2. $C_{12}H_{13}O_4NS$ requires C, 55·95; H, 4·9; N, 5·5%). The compound (0·2 g.), when mixed with benzylamine (0·5 g.), became hot; after 2—3 mins., addition of 2N-hydrochloric acid gave N-*monothiocarbobenzyloxyglycine benzylamide* (X) (0·2 g.), which separated from ethyl acetate–light petroleum in needles, m. p. 153° (Found: C, 65·3; H, 5·9; N, 9·05. $C_{17}H_{18}O_3N_2S$ requires C, 65·0; H, 5·8; N, 8·9%). When the acid (IX) was heated at 100° with acetic anhydride (5—8 parts) and the reagent removed in a vacuum the *anhydride* (XII) was obtained; it separated from ethyl acetate in needles, m. p. 158° (Found: C, 55·5; H, 4·7; N, 6·5. $C_{20}H_{20}O_6N_2S_2$ requires C, 55·5; H, 4·7; N, 6·5).

N-*Dithiocarbobenzyloxy-ββ-diethoxyalanine.*—ββ-Diethoxyalanine (2·12 g.) in water (7 c.c.) containing potassium hydroxide (1·4 g.) was shaken with carbon disulphide (1 g.), and the clear solution further shaken with benzyl chloride (1·5 g.) overnight. Unchanged reagent was extracted with ether and an oil precipitated from the aqueous phase with hydrochloric acid. When this was taken up in benzene, and light petroleum added N-*dithiocarbobenzyloxy-ββ-diethoxyalanine* (XIV) crystallised; it recrystallised from chloroform–light petroleum in needles, m. p. 79° (yield 0·5 g.) (Found: C, 49·85; H, 6·55; N, 4·1. $C_{15}H_{21}O_4NS_2,H_2O$ requires C, 49·85; H, 6·4; N, 3·9%). On one occasion a less soluble unidentified by-product was obtained in small quantity; it crystallised from benzene in needles, m. p. 160° (Found: C, 50·8; H, 5·2%).

The preceding acid (2·5 g.) was treated with excess of ethereal diazomethane. Evaporation of the ether in a vacuum gave a syrup which slowly crystallised. N-*Dithiocarbobenzyloxy-ββ-diethoxyalanine methyl ester* crystallised from ethanol–water in white needles, m. p. 46° (yield 1·5 g.) (Found: C, 54·1; H, 6·5; N, 3·9. $C_{16}H_{23}O_4NS_2$ requires C, 53·75; H, 6·5; N, 3·9%).

The acid (XIV) (0·36 g.), acetic anhydride (3 c.c.), and pyridine (0·2 c.c.) were mixed and heated at 40° for 5 mins. The cooled solution was added to water (10 c.c.) to precipitate a dark oil which crystallised after 24 hours. 2-*Benzylthio-4-carboxythiazole* (XV) crystallised from chloroform–light petroleum in yellow needles, m. p. 187—189° (decomp.) (yield, 0·15 g.) (Found: C, 52·7; H, 3·4; N, 5·7. $C_{11}H_9O_2NS_2$ requires C, 52·6; H, 3·6; N, 5·6%).

Derivatives of 2-Mercaptothiazolone.—*N*-Dithiocarbethoxyglycine (2·3 g.), benzaldehyde (1·4 g.) and acetic anhydride (5·0 g.) were heated at 90° for 15 mins., and excess of reagent removed in a vacuum. The residue of 2-*ethylthio-4-benzylidenethiazolone* (XVI) crystallised, and it recrystallised from acetone–water in rhombic plates, m. p. 62—64° (yield, after 3 crystallisations, 1·5 g.) (Found: C, 57·8; H, 4·8; N, 5·75. $C_{12}H_{11}ONS_2$ requires C, 57·8; H, 4·5; N, 5·6%); light absorption (chloroform): max. at 243, 280, 372 mμ; E_1^1 = 350, 310, 1000, respectively. Dithiocarbethoxyglycine (1·0 g.) in ether was kept for 2 days with phosphorus tribromide (1·6 g.), and the oily crystals washed with more ether by decantation. Shaking the crystals with aqueous sodium acetate gave an oil which was taken up in ether and treated directly with benzylamine, whereupon the solvent boiled and ethylthiol was evolved. Very large rhombic plates slowly separated, and more product was obtained on evaporating the filtrate and rubbing the residue with hydrochloric acid. The dibenzylamide (V) crystallised from ethyl acetate–light petroleum, chloroform–light petroleum, or less satisfactorily from acetone–water or methanol–water in plates or rosettes, m. p. 145—146°, identical with the earlier material.

2-Benzylthiothiazolone (VIII) (0·5 g.), ethyl orthoformate (0·5 g.), and acetic anhydride (10 c.c.) were warmed together to 100° for 20 mins., and excess reagent and solvent removed in a vacuum. The dark residual oil was distilled at 50° in a high vacuum and then solidified; it was recrystallised from light petroleum. 2-*Benzylthio-4-ethoxymethylenethiazolone* (XVII; R = OEt) separated in colourless prisms, m. p. 57° (yield, 0·4 g.) (Found: C, 55·9; H, 4·7; N, 5·2. $C_{13}H_{13}O_2NS_2$ requires C, 55·9; H, 4·7; N, 5·0%). The same compound was also obtained as follows: *N*-Dithiocarbobenzyloxy-ββ-diethoxyalanine (0·5 g.) and acetic anhydride (5 c.c.) were heated to 100° for 15 mins., and excess of solvent removed in a vacuum. On refluxing the residue with light petroleum (25 c.c.) and cooling the filtrate, the ethoxymethylene compound (0·2 g.) separated in prisms, m. p. 57°, which did not depress the m. p. of the former product. Light absorption (chloroform): Max. at 241, 260, 328 mμ; E_1^1 = 800, 1000, 1050 respectively.

The ethoxymethylene compound (0·2 g.) was treated with aniline (0·08 g.) in ethanol. Yellow crystals began to be deposited after a few seconds and were collected after 30 mins. 2-*Benzylthio-4-anilinomethylenethiazolone* (XVIII) separated from ethanol in lemon-yellow laths, m. p 118° (Found: C, 62·5; H, 4·3; N, 8·9. $C_{17}H_{14}ON_2S_2$ requires C, 62·5; H, 4·3; N, 8·6%). The compound (XVIII) (0·2 g.) was shaken with 2N-sodium hydroxide (3 c.c.) at room temperature, and the filtrate was diluted to 10 c.c. and acidified. 2-*Benzylthio-4-hydroxymethylenethiazolone* (XVII; R = OH) (yield, 0·13 g.) separated from aqueous acetone in clusters of small white needles, m. p. 146—147° (decomp.) (Found: C, 52·55; H, 3·7; N, 5·55. $C_{11}H_9O_2NS_2$ requires C, 52·55; H, 3·6; N, 5·55%). The compound (XVII; R = OEt) (0·15 g.) was added to sulphanilamide (0·09 g.) in warm ethanol (5 c.c.). The solution rapidly became yellow and within a few minutes yellow needles separated. The *derivative*, probably (XIX), recrystallised from aqueous acetone, formed yellow needles, m. p. 207—208° (Found: C, 50·55; H, 4·64; N, 8·9. $C_{19}H_{21}O_4N_3S_2$ requires C, 50·55; H, 4·7; N, 9·3%). The same compound resulted from reaction in propanol.

Miscellaneous Reactions.—Ethyl aminomalonate (6 g.) was shaken for 3 hours with carbon disulphide (3 c.c.), and the solution treated with potassium hydroxide (1·6 g.) in water (10 c.c.) and again shaken for 2½ hours with benzyl chloride (4·4 g.). The heavy oil was taken up in ether, freed from acidic impurity, and solvent removed. On standing with light petroleum the oil crystallised. *Ethyl* N-*dithiocarbobenzyloxyaminomalonate* (XX) separated from light petroleum in colourless plates, m. p. 71° (Found: C, 52·8; H, 5·65; N, 4·2. $C_{15}H_{19}O_4NS_2$ requires C, 52·8; H, 5·6; N, 4·1%).

N-Dithiocarbobenzyloxyglycine (2·0 g.), benzaldehyde (0·9 g.), and acetic anhydride (10 c.c.) were heated to 100° for 20 mins. After removal of solvent in a vacuum the residue crystallised completely

and was almost pure (m. p. 120—121°). 2-*Benzylthio*-4-*benzylidenethiazolone* (XVII; R = Ph) separated from chloroform–light petroleum in long pale yellow needles, m. p. 121° (Found: C, 65·2; H, 4·1; N, 4·7. $C_{17}H_{13}ONS_2$ requires C, 65·5; H, 4·2; N, 4·5%).

Glycine (5 g.) in water (6·6 c.c.) and potassium hydroxide (7·7 g.) in water (10 c.c.) were mixed, and the ice-cold solution shaken with carbon disulphide (5·1 g.) until a clear brown solution was obtained. The solution was cooled, stirred, and ethyl chloroformate (7·2 g.) added dropwise. A thick white precipitate soon appeared. The solid was dissolved in water, and the solution acidified, giving a white crystalline precipitate. N-*Dithiocarbocarbethoxyglycine* (XXI) crystallised from ether–light petroleum in white needles, m. p. 125° (yield, 4 g.) (Found: C, 32·6; H, 4·0; N, 6·3. $C_6H_9O_4NS_2$ requires C, 32·2; H, 4·0; N, 6·3%).

The preceding acid (5 g.), ethyl orthoformate (7 c.c.) and acetic anhydride (40 c.c.) were heated on the steam-bath for 30 mins. The solvents were removed in a vacuum to leave a dark oil which crystallised on cooling. 2-*Carbethoxythio*-4-*ethoxymethylenethiazolone* crystallised from petroleum (b. p. 60—80°) as white needles, m. p. 83° (yield, 2 g.) (Found: C, 41·1; H, 4·4. $C_9H_{11}O_4NS_2$ requires C, 41·4; H, 4·2%).

N-Dithiocarbethoxyglycine (9 g.) was heated to 100° for 15 mins. with acetic anhydride (22 c.c.), excess of which was then removed in a vacuum. Residual 2-ethylthiothiazolone distilled as an oil at 40—70° in a high vacuum. When the dithio-acid (2·6 g.), acetic anhydride (4·0 c.c.), and ethyl orthoformate (2·5 g.) were heated to 100° for 20 mins. the solution became purple and the residue, on removal of excess of reactants in a vacuum, crystallised. The coloured impurity was removed by crystallisation from light petroleum (charcoal), 2-*ethylthio*-4-*ethoxymethylenethiazolone* being obtained in colourless plates, m. p. 65—66° (Found: C, 44·4; H, 5·4. $C_8H_{11}O_2NS_2$ requires C, 44·2; H, 5·1%). The ethoxymethylene compound (1 g.) was shaken with potassium hydroxide (10 c.c.) for one hour, and the solution then acidified. 2-*Ethylthio*-4-*hydroxymethylenethiazolone* (yield, 0·7 g.) separated from petroleum (b. p. 60—80°) as white needles, m. p. 100° (Found: C, 38·4; H, 3·9; N, 7·6. $C_6H_7O_2NS_2$ requires C, 38·1; H, 3·7; N, 7·4%).

Penicillenic Acid Analogues, etc.—Penicillamine hydrochloride (0·2 g.), 2-benzylthio-4-ethoxymethylenethiazolone (0·3 g.) and aqueous sodium hydroxide (24·5 c.c.; 0·088N) were shaken together for 4 hours. The reddish solution, which no longer gave thiol colour reactions, was decolorised with charcoal in the cold and acidified with hydrochloric acid (2·0 c.c.; 2N). The solid (0·25 g.) was purified by repeated solution in aqueous sodium hydrogen carbonate and acidification, the penicillenic acid *analogue* forming a solid, m. p. 85° (decomp.) (Found: C, 50·2; H, 3·1; N, 7·0. $C_{16}H_{16}O_3N_2S_3$ requires C, 50·2; H, 4·8; N, 7·3%). Penicillamine methyl ester (0·67 g.) was added to 4-ethoxymethylene-2-benzylthiothiazolone (0·95 g.) in ethanol (4 c.c.). Thiol reactions were no longer given by the solution after a few minutes, and it was evaporated in a vacuum and the gum chromatographed in chloroform on alumina. The pale yellow gum obtained from the filtrate solidified on rubbing with a little methanol to a white powder (yield, 1·0 g., m. p. 108—110°). The *methyl* ester analogue (XXII; R = CH_2Ph) of the above acid separated from aqueous methanol in needles, m. p. 110° (Found: C, 51·55; H, 5·1; N, 6·85. $C_{17}H_{20}O_3N_2S_3$ requires C, 51·5; H, 4·9; N, 7·0%). Light absorption (chloroform): Max. at 251—256, 281, 359 mμ; E_1^1 = 370, 180, 520, respectively. Similarly, penicillamine methyl ester (1·07 g.) and 4-ethoxymethylene-2-ethylthiothiazolone (1·4 g.) gave the *ethylthio*-ester (XXII; R = Et), which crystallised from petroleum (b. p. 60—80°) in rectangular prisms, m. p. 83° (yield, 1·0 g.) (Found: C, 43·0; H, 5·6; N, 8·4. $C_{12}H_{18}O_3N_2S_3$ requires C, 43·1; H, 5·4; N, 8·4%).

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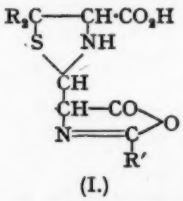
210. *Studies in the Azole Series. Part V. A Synthesis of β-Phenylcysteine.*

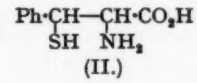
By A. H. COOK, G. HARRIS, and SIR IAN HEILBRON.

Exploratory routes to β-phenylcysteine (which was required in attempts to synthesise a penicillin analogue) by conventional means *via* 2-phenyl-4-benzylideneoxazolone, and α-aminocinnamic acid derivatives were unsuccessful. 2-Ethylthio-4-benzylidenethiazolone (cf. preceding paper) was, however, converted by three routes into derivatives of 4-carboxy-5-phenyl-2-thiazolidone (XVIII) which were hydrolysed to the required mercaptoamino-acid.

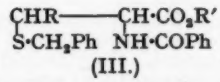
THE literature on attempted syntheses of penicillin and its analogues records many attempts to obtain the thiazolidine-oxazolone structure (I), starting both from penicillamine and from



(I.)



(II.)

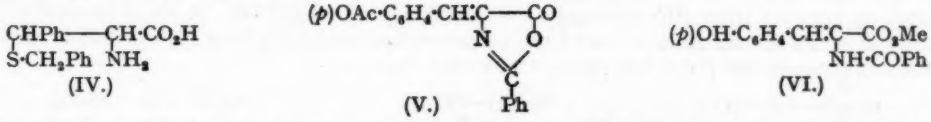


(III.)

cysteine. Work with numerous derivatives of these mercaptoamino-acids has, however, demonstrated the difficulty of obtaining the combined heterocyclic systems, and the final

products have so far mostly been of the penicilloate or penicillenate type (*Nature*, **1945**, **156**, 766; *Science*, **1945**, **102**, 622). The present work had for its eventual object the preparation of a thiazolidine-oxazolone and other formulations for the penicillins from β-phenylcysteine (II).

The route by which other mercaptoamino-acids, including penicillamine, are available was first explored. 2-Phenyl-4-benzylideneoxazolone reacted readily with benzylthiol in methanolic sodium methoxide to give the *ester* (III; R = Ph, R′ = Me) in excellent yield. Only one of the two possible stereoisomeric esters was obtained, and this was hydrolysed to β-*phenyl*-S-*benzylcysteine* (IV). On reduction of this with sodium in liquid ammonia, benzylthiol was regenerated, showing that fission of the molecule had taken place on the undesired side of the sulphur atom, and the sole acid product isolated was β-phenylalanine [(IV) may be regarded as a substituted dibenzyl sulphide, fission of which depends upon the particular nature of the substituents]. *p*-Hydroxybenzaldehyde has also been condensed with hippuric acid under acetylating conditions to give 2-phenyl-4-*p*-acetoxybenzylideneoxazolone (V), previously described by Erlenmeyer and Halsey (*Annalen*, 1899, **307**, 139). Attempts to prepare the cysteine derivative (III; R = *p*-OH·C_6H_4, R′ = Me) by reaction of (V) with benzylthiol in presence of methanolic sodium methoxide were not successful however, the product consisting of the *ester* (VI).

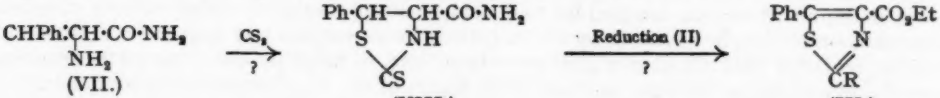


(IV.) (V.) (VI.)

It was clear that a route which evaded the reduction of the *S*-benzyl compound would have to be used, and additions of hydrogen sulphide and thioacetic acid to appropriate amino-acid derivatives were examined. Treatment of 4-benzylidene-2-methyloxazolone with hydrogen sulphide in methanolic sodium methoxide resulted only in the formation of methyl α-acetamidocinnamate, and attempts to add hydrogen sulphide or thioacetic acid to this ester or its corresponding acid under various conditions were also unsuccessful.

An unsuccessful route, which was examined, consisted in reaction of the amide (VII) of α-aminocinnamic acid (Braucke, *Rec. Trav. chim.*, 1896, **15**, 131) with carbon disulphide in the hope of forming (VIII) which might have been reduced; a similar route to penicillamine starting from α-amino-ββ-dimethylacrylic esters has been described in a penicillin report which has now been published (Cook, Heilbron, and Shaw, CPS 311).

Attempts were made to reduce suitable thiazoles to derivatives of (II). Ethyl β-bromo-β-phenylpyruvate (Gault and Wieck, *Bull. Soc. chim.*, 1922, **31**, 881) was easily condensed with thiourea to the *aminothiazole* (IX; R = NH_2) and with thiobenzamide to the *diphenylthiazole* (IX; R = Ph) (cf. Erlenmeyer and Morel, *Helv. Chim. Acta*, 1942, **25**, 1073, where similar reactions with ethyl bromopyruvate are described). These thiazoles were characterised as their *picrates* and by alkaline hydrolysis to the corresponding *acids*. Treatment of (IX; R = NH_2) with sodium amalgam failed to give a reduced product, yielding only an unidentified isomer of the original amino-compound, while similar treatment of (IX; R = Ph) furnished

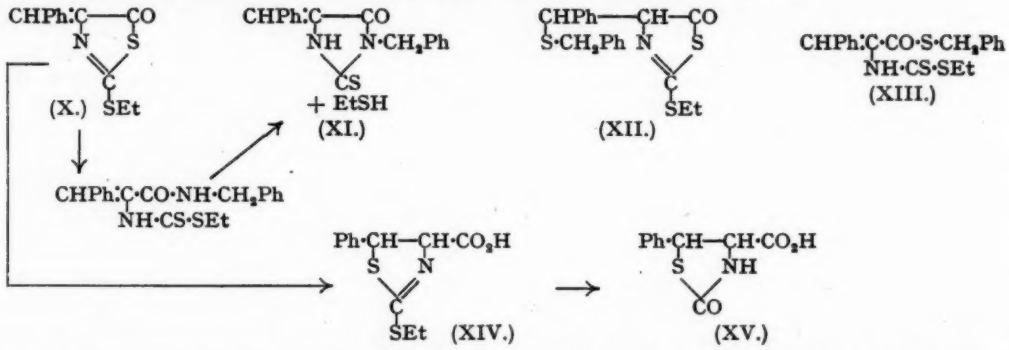


(VII.) (VIII.) (IX.)

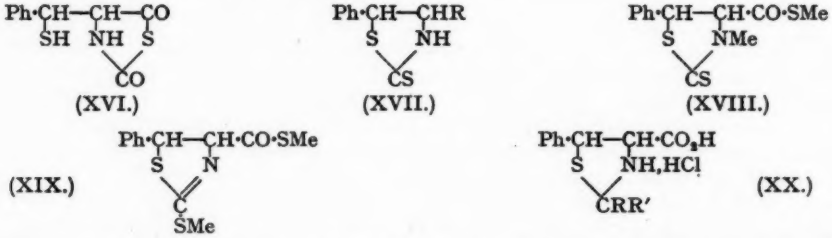
benzaldehyde, presumably as a result of fission of the primary product, and a compound which gave a mercury derivative and the ferric chloride and nitroprusside colour reactions expected of (II); this material was, however, not obtained pure.

2-Ethyl- and 2-benzyl-thio-4-benzylidenethiazol-5-one were described in the preceding paper, and attention was turned to these as possibly affording intermediates which might be more useful. As described in the preceding paper, the ethyl compound (X) exhibited a rather unexpected reactivity; with cold ethereal benzylamine ready reaction ensued with elimination of ethylthiol, the *thiohydantoin* (XI) being formed, perhaps in the manner indicated. On the other hand, the thiazolone (X) reacted with benzylthiol to give a compound first considered to be the thiazolone (XII) but probably correctly formulated as the *thio-ester* (XIII) since, on reaction with benzylamine, it was converted into the thiohydantoin (XI). A similar ring fission was observed on boiling (X) with aqueous ethanolic alkali, whereby it was converted into an acid with simultaneous loss of ethylthiol. The crystalline acid still contained sulphur and was

formulated as **4-*carboxy*-5-*phenylthiazolid*-2-*one*** (XV) formed *via* (XIV); (XV) yielded one form of the required β-phenylcysteine on hydrolysis but only in poor overall yield.



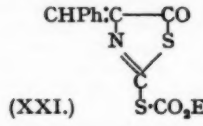
When (X) was treated in methanolic sodium methoxide with hydrogen sulphide reaction was sluggish as inferred from the extremely slow evolution of ethylthiol. A small quantity of a crystalline *substance* was isolated and from its properties may have been (XVI), but in view of its difficult accessibility it did not appear to be very useful.



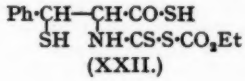
The addition of hydrogen sulphide to (X) in the presence of methanolic triethylamine, however, resulted in rapid elimination of ethylthiol, and the product was an acid, $C_{10}H_9ONS_3$, obtained as its ***triethylamine*** salt, which must be formulated as the ***thiothiazolidone*** (XVII; R = CO·SH). On being heated with dilute hydrochloric acid this yielded a stable acid, $C_{10}H_9O_2NS_3$, which is to be represented as **4-*carboxy*-5-*phenyl*-2-*thiothiazolidone*** (XVII; R = CO_2H). (XVII; R = CO·SH) was further characterised by reaction with diazomethane and with diazomethane followed by methyl sulphate, being so converted into two ***dimethyl*** derivatives, (XVIII) and (XIX), which structures are supported by the experimental conditions employed. (XVII; R = CO_2H) is exactly comparable with an intermediate which afforded penicillamine by reduction, and was indeed sought earlier with the intention of submitting it to reduction. Extensive attempts were therefore made to convert it into β-phenylcysteine [reduction with sodium in liquid ammonia, aluminium and acid, sodium amalgam under various conditions, stannous chloride (*e.g.*, in butanol), by electrolytic reduction commonly applicable to thioamides, as well as by fairly mild alkaline or acid hydrolysis] but, to judge by the weak colour reaction of the products with ferric chloride, no more than traces of the required mercaptoamino-acid were formed. After these abortive efforts it was found that the hydrolytic fission of (XVII; R = CO_2H) could be effected surprisingly cleanly by heating for several hours with concentrated hydrochloric acid under pressure (cf. Gabriel and Posner, *Ber.*, 1894, **27**, 3509). The product was a thiol giving the anticipated intense indigo-blue colour with ferric chloride, and also an α-amino-acid hydrochloride giving a red-purple ninhydrin reaction; analysis left no doubt of its formulation as **β-*phenylcysteine hydrochloride***, apparently only one of the two possible stereoisomerides being formed. Like other acids of its class, it reacted readily with carbonyl compounds with disappearance of the thiol grouping, and was characterised as its product with acetone, **4-*carboxy*-5-*phenyl*-2 : 2-*dimethylthiazolidine hydrochloride*** (XX; R = R′ = Me) and with benzaldehyde, **4-*carboxy*-2 : 5-*diphenylthiazolidine hydrochloride*** (XX; R = H, R′ = Ph).

Before this synthesis had been completed, other routes which might have proceeded through more readily hydrolysable intermediates had been projected. For instance, dithiocarbocarbethoxyglycine (preceding paper), with benzaldehyde in presence of acetic anhydride, afforded **2-*carbethoxythio*-4-*benzylidenethiazolone*** (XXI); it was expected that treatment of the latter

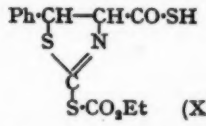
with hydrogen sulphide would lead to either (XXII) or (XXIII). Treatment of the former with alkali, followed by acidification, would have yielded phenylcysteine; or reduction of the



(XXI.)



(XXII.)



(XXIII.)

latter with aluminium amalgam, followed by acid hydrolysis or treatment with mercuric chloride, would have yielded the same product. In fact, however, it was found that treatment with hydrogen sulphide in a basic medium yielded (XVII; R = CO·SH) by loss of carbon dioxide and ethylthiol.

Experimental.

Experiments with Oxazolones.—2-Phenyl-4-benzylideneoxazolone (Erlenmeyer *et al.*, *Annalen*, 1893, **275**, 3; 1904, **337**, 266) (50 g.) in dry methanol (500 c.c.) containing sodium methoxide (11 g.) was slowly treated with benzylthiol (25 g.); much solid had separated after 2 hours' stirring but the suspension was kept overnight, filtered, and the product washed well with methanol. The crude *methyl* ester of *N-benzoyl-β-phenyl-S-benzylcysteine* (yield 76 g., 98%) was practically insoluble in methanol but separated in needles, m. p. 164°, from dioxan–water or chloroform–light petroleum (Found: C, 71·0; H, 5·6; N, 3·75. $C_{24}H_{23}O_3NS$ requires C, 71·1; H, 5·7; N, 3·5%). This ester (165 g.) was refluxed for 2½ hours with water (375 c.c.) and 50% hydrogen bromide in acetic acid (750 c.c.) and acetic acid (375 c.c.). The solution was evaporated to small bulk and the residue stirred with ether. The filtered aqueous solution was diluted to 3 l. and further extracted with ether to remove benzoic acid after adding concentrated hydrochloric acid (100 c.c.). Adjustment of the aqueous solution to pH 7 with ammonia gave *β-phenyl-S-benzylcysteine* (69 g., 55%); it was insoluble in common organic solvents except warm acetic acid, but separated in needles, m. p. 181—185° (sintering at 175°), from acetic acid in ether (Found: N, 5·1, 5·1. $C_{16}H_{17}O_2NS$ requires N, 4·9%). The foregoing *S*-benzyl compound (10 g.) in liquid ammonia (500 c.c.) was reduced in the normal manner with sodium (2·5 g., 3 equivs.); ammonium chloride (7 g.) was added, and ammonia removed, the dry residue being stirred with ethereal hydrogen chloride and then with cold ethanol (100 c.c.). Removal of solvent from the alcoholic filtrate gave an amino-acid hydrochloride (ninhydrin reaction) which, however, contained no sulphur (yield, 5·4 g.). It crystallised from concentrated hydrochloric acid or ethanol–ether in rectangular plates, m. p. 230° (decomp.), and was evidently β-phenylalanine hydrochloride (Found: C, 53·4; H, 5·7; N, 6·6. Calc. for $C_9H_{12}O_2NCl$: C, 53·6; H, 6·0; N, 6·9%); it afforded free phenylalanine identical with this material obtained by literature methods.

p-Hydroxybenzaldehyde (34 g.), anhydrous sodium acetate (23 g.), acetic anhydride (120 g.), and hippuric acid (50 g.) were warmed on the steam-bath for 1 hour though the reaction mixture set to a solid mass within 5 mins. The product was filtered off, washed with acetic acid, and crystallised from the same solvent. 2-Phenyl-4-*p*-acetoxybenzylideneoxazolone separated in pale yellow needles, m. p. 179°, from acetic acid or chloroform (Found: C, 70·0; H, 4·3; N, 4·6. Calc. for $C_{18}H_{13}O_4N$: C, 70·3; H, 4·3; N, 4·6%) (yield 63 g., 73%). The azlactone (20 g.) in methanol (250 c.c.) containing sodium methoxide (3·5 g.) was kept for 3—4 days with benzylthiol (8·5 g.). Acidification (Congo-red), evaporation in a vacuum, and rubbing the residue with water gave a crystalline solid (16·1 g.). This was a mixture eventually separated by crystallisation from acetone–light petroleum. The less soluble component was identified as dibenzyl disulphide; it separated from acetone–water or ethanol in prismatic needles, m. p. 69—73° (Found: C, 67·9; H, 5·7. Calc. for $C_{14}H_{14}S_2$: C, 68·3; H, 5·7%). The more soluble *ester* (V) crystallised from acetone–light petroleum in hexagonal prisms, m. p. 184—185° (Found: C, 68·6; H, 5·2; N, 5·0. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1; N, 4·7%).

Experiments with Derivatives of α-Aminocinnamic Acid.—4-Benzylidene-2-methyloxazolone (Raiford and Burman, *J. Org. Chem.*, 1943, **8**, 469) (40 g.) in dry methanol (450 c.c.) containing sodium methoxide (6 g.) was treated overnight with hydrogen sulphide at 0°. The solution was neutralised and evaporated in a vacuum, and the residues stirred with water. The crystalline product was washed well with ether (yield 28 g.) and crystallised from chloroform–light petroleum to give *methyl α-acetamidocinnamate* in laths, m. p. 125° (softening at 122°) (Found: C, 65·4; H, 6·1; N, 6·2. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4%). Attempts to add thioacetic acid or hydrogen sulphide as such or as sodium sulphide to this ester at 105—120° for 15—20 hours led either to no change or to formation of α-acetamidocinnamic acid.

Ethyl αβ-dibromo-β-phenylpropionate (90 g.) was shaken for 3 days at 45—60° with ammonia (500 c.c., *d* 0·880). On cooling and standing, the crude *α-amino-β-phenylacrylamide* separated and was fractionally crystallised from acetone–light petroleum. The less soluble crops comprised the known amide, m. p. 170—176° (Braucke, *loc. cit.*, gives m. p. 172°); the more soluble crops provided an *isomeride*, which separated from chloroform–light petroleum in rhombic plates, m. p. 122—124° (Found: C, 66·3; H, 6·3; N, 17·1. $C_9H_{10}ON_2$ requires C, 66·6; H, 6·2; N, 17·3%); the total yield was 21·9 g. (51%).

Experiments on Selected Thiazoles.—Ethyl β-bromo-β-phenylpyruvate (Gault and Wieck, *loc. cit.*) (10 g.) was added to thiourea (5 g.) in hot ethanol (70 c.c.), and reaction completed by heating for 5 mins. on the steam-bath. The thiazole was precipitated by pouring into 25% aqueous ammonia (200 c.c.), and recrystallised from dilute ethanol (yield, 10·5 g.). *2-Amino-4-carbethoxy-5-phenylthiazole* (IX; R = NH_2) separated in colourless plates, m. p. 182° (Found: C, 57·8; H, 4·9; N, 11·4. $C_{12}H_{12}O_2N_2S$ requires C, 58·1; H, 4·9; N, 11·3%); its *picrate* separated from methanol in needles, m. p. 201° (Found: N, 14·7. $C_{18}H_{15}O_9N_5S$ requires N, 14·7%). The thiazole ester (0·5 g.) in water (20 c.c.) containing

ethanol (2 c.c.) was treated with 3% sodium amalgam (17 g.). On completion of the reaction the aqueous solution was allowed to stand and the *isomeride* of (IX; R = NH_2) (400 mg.) collected; it separated from methanol–water in thin colourless needles, m. p. 202°, which depressed the m. p. of the initial compound (Found: C, 57·9; H, 4·9; N, 11·3%); its *picrate* separated from ethanol in needles, m. p. 194°, which depressed the m. p. of the picrate described above (Found: N, 14·8%). The amine (IX; R = NH_2) was hydrolysed with hot aqueous-ethanolic potassium hydroxide during 20 mins. Acidification with acetic acid yielded an acid. Recrystallised from ethanol, *2-amino-4-carboxy-5-phenylthiazole* separated as colourless needles, m. p. 225—226° (decomp.) (Found: C, 54·6; H, 3·8; N, 12·9. $C_{10}H_8O_2N_2S$ requires C, 54·5; H, 3·7; N, 12·7%).

Ethyl β-bromo-β-phenylpyruvate (1 g.) and thiobenzamide (0·5 g.) were heated in refluxing ethanol (10 c.c.) for 30 mins., and on cooling, the thiazole (0·8 g.) separated. *4-Carbethoxy-2 : 5-diphenylthiazole* (IX; R = Ph) crystallised from ethanol in colourless needles, m. p. 110—111° (Found: C, 69·9; H, 5·3; N, 4·5. $C_{18}H_{15}O_2NS$ requires C, 69·9; H, 4·9; N, 4·5%). *4-Carboxy-2 : 5-diphenylthiazole*, obtained from this as for the above thiazole acid, crystallised from aqueous ethanol as colourless needles, m. p. 140—141° (Found: C, 67·9; H, 4·0; N, 5·3. $C_{16}H_{11}O_2NS$ requires C, 68·3; H, 4·0; N, 5·0%).

Experiments with 2-Ethylthio-4-benzylidenethiazol-5-one (CPS 440).—The thiazolone (5 g.) in methanol (100 c.c.) containing sodium methoxide (1·0 g.) was saturated with hydrogen sulphide at 0° for *ca.* 16 hours, and the solution then evaporated at a low temperature. Extraction of the residue with chloroform and concentration of the extract gave crystals which, recrystallised from toluene, separated as platelets, m. p. 145—148° (decomp.); this product was not acidic and was probably the slightly impure *thiazolidione* (XVI) (Found: C, 49·3; H, 4·1; N, 5·6. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·8%). It could not be hydrolysed to the required mercaptoamino-acid. The mother-liquors from the preceding compound reacted with benzylamine to give 1-benzyl-4-benzylidenethiohydantoin, which separated from chloroform–light petroleum in rhombic plates, m. p. 226—227°. This compound had been previously obtained from the original thiazolone. 2-Ethylthio-4-benzylidenethiazol-5-one (0·2 g.) was treated in ether with excess of benzylamine, ethylthiol being evolved. After 1 hour, removal of ether and addition of water gave a yellow solid. On repeated crystallisation from chloroform–light petroleum *1-benzyl-4-benzylidene-2-thiohydantoin* (XIV) was obtained in long rhombic plates, m. p. 226—227° (Found: C, 69·2; H, 4·7; N, 9·1. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·7; N, 9·5%).

2-Ethylthio-4-benzylidenethiazol-5-one (1 g.) was boiled with 1N-sodium hydroxide (4·2 c.c.) and a little ethanol until dissolved (2 hours), ethylthiol being evolved. Ethanol was removed in a vacuum, unchanged thiazolone extracted with ether, and the aqueous solution acidified and extracted with chloroform. On removal of solvent, and rubbing the residue with ether–light petroleum it solidified. *4-Carboxy-5-phenyl-2-thiazolidone* separated, after repeated crystallisation from chloroform–light petroleum, in platelets, m. p. 157—158° (Found: C, 51·6; H, 4·1; N, 5·7. $C_{10}H_9O_3NS,\frac{1}{2}H_2O$ requires C, 51·7; H, 4·3; N, 6·0%). It yielded β-phenylcysteine on hydrolysis with concentrated hydrochloric acid (sealed tube).

2-Ethylthio-4-benzylidenethiazol-5-one (5 g.) was stirred with methanol (80 c.c.) containing sodium methoxide (50 mg.) and benzylthiol (2·5 g.) for 2 hours, a clear solution being obtained. The sodium methoxide was neutralised with hydrochloric acid, and the solution evaporated to dryness in a vacuum. The residual oil was distilled repeatedly in a high vacuum at 100—110° (bath temp.) as a pale yellow, mobile oil, regarded as the *thio*-ester (XIII) (Found: C, 60·9; H, 5·4; N, 4·2. $C_{19}H_{19}ONS_2$ requires C, 61·1; H, 5·1; N, 3·8%). Vigorous reaction occurred on treating the ester with excess of ethereal benzylamine. The product, recrystallised from ethyl acetate, separated as pale yellow prisms, m. p. 227°, undepressed by 1-benzyl-4-benzylidene-2-thiohydantoin prepared as above. The original ethylthiothiazolone (5 g.) in methanol (100 c.c.) containing triethylamine (2 g.) was saturated with hydrogen sulphide at 0° for 20 hours, and the solution just neutralised with dilute hydrochloric acid. On scratching and cooling, white crystals (3·9 g.) of an acid separated; it was soluble in ethanol, acetone, or dioxan, and crystallised from chloroform containing a little methanol, but was better purified by solution in aqueous sodium hydrogen carbonate and precipitation with acid, or by precipitation from ethyl acetate with light petroleum. *4-Thiocarboxy-5-phenyl-2-thiothiazolidone* (XVII; R = CO·SH) had m. p. 157—158°, resolidifying and melting again at 180—190° (Found: C, 47·2; H, 3·8; S, 37·6. $C_{10}H_9ONS_3$ requires C, 47·1; H, 3·5; S, 37·6%). The *triethylamine* salt, which provided the best means of isolating the acid in the above preparation (yield, 78%), crystallised from chloroform–light petroleum in rhomboidal prisms, m. p. 132—133° (decomp.) (Found: C, 53·9; H, 7·1; N, 7·7. $C_{16}H_{24}ON_2S_3$ requires C, 53·9; H, 6·8; N, 7·9%). The preceding thiol-acid (2 g.) in acetone was treated with excess of diazomethane in ether. After the reaction, solvents were removed, and the oil deposited crystals on dissolution in acetone and addition of light petroleum. The crystals were no longer acid, and crystallised from chloroform–light petroleum in long laths, m. p. 134—136°, consisting of the *dimethyl* derivative (XVIII) (Found: C, 50·6; H, 4·7; N, 5·0. $C_{12}H_{13}ONS_3$ requires C, 50·9; H, 4·6; N, 5·0%). The oil obtained by removal of solvents from the filtrate was treated with 1 mol. of sodium hydroxided an methyl sulphate in ether. Removal of ether gave an oil, which was distilled in a high vacuum. Upon standing, the distillate crystallised. Recrystallisation from ethanol and water yielded the *compound* (XIX) as octahedra, m. p. 74° (Found: C, 51·0; H, 4·8; N, 4·9. $C_{12}H_{13}ONS_3$ requires C, 50·9; H, 4·6; N, 5·0%).

The thiol-acid (XVII; R = CO·SH) (20 g.) was heated with 2N-hydrochloric acid at 90° for 30 minutes, *i.e.*, until evolution of hydrogen sulphide ceased. The cold solution was decanted from the heavy orange oil, which was then stirred with ether. On evaporation of the ether and treatment of the gum with a little chloroform, the material crystallised but retained gum which was only removed on triturating with solvents. The solid was soluble in chloroform or ethyl acetate, sparingly soluble in ether or light petroleum; it was further purified by solution in aqueous sodium hydrogen carbonate and precipitation with acid, and recrystallisation from ethanol–light petroleum. *4-Carboxy-5-phenyl-2-thiothiazolidone* (XVII; R = CO_2H) separated in very small laths, m. p. 173—175° (Found: C, 50·6; H, 3·9; N, 5·8. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·9%); a further quantity was eventually obtained from the original acid hydrolysate by standing at 0° (total yield, 10·1 g.).

β-Phenylcysteine.—The preceding acid (5·9 g.) was heated for 13 hours with concentrated hydrochloric

acid (50 c.c.) at 100° (sealed tube). Much hydrogen sulphide was generated and, on cooling, a solid hydrochloride separated (3·7 g.). This was dried over phosphoric oxide to remove water of crystallisation and recrystallised from *iso*propanol containing a little light petroleum. *β-Phenylcysteine hydrochloride* separated in platelets, m. p. 202—203° (decomp.) (Found: C, 46·6; H, 5·4; N, 5·8. $C_9H_{12}O_2NClS$ requires C, 46·4; H, 5·2; N, 6·0%). The hydrochloride was slightly soluble in *iso*propanol, cold water, hot or cold acetone, chloroform, or *tert.*-butanol, but was easily soluble in ethanol. Like penicillamine, it gave an intense blue colour with ferric chloride and a red-purple ninhydrin reaction. The hydrochloride (0·5 g.) in hot ethanol (11 c.c.) was refluxed with acetone (20 c.c.) for 20 minutes, test portions then no longer giving thiol colour reactions. The solution was evaporated in a vacuum, and the residue repeatedly treated with ethereal hydrogen chloride. It was recrystallised several times from chloroform containing a little methanol by addition of ether, with rejection of a little gummy material which separated first, and *4-carboxy-5-phenyl-2 : 2-dimethylthiazolidine hydrochloride* separated in clusters of prisms, m. p. 195° (decomp.) (Found: C, 50·2; H, 6·4; N, 4·7. $C_{13}H_{16}O_2NClS$,MeOH requires C, 50·2; H, 6·5; N, 4·6%); it was soluble in water and very soluble in methanol but sparingly soluble in chloroform. It regenerated β-phenylcysteine by boiling in 2N-hydrochloric acid for a few minutes.

β-Phenylcysteine hydrochloride (0·5 g.), benzaldehyde (0·3 g.), and a few drops of methanol were heated on the steam-bath for 3 mins., after which the resin was broken down to a white powder on rubbing with dry ether. *4-Carboxy-2 : 5-diphenylthiazolidine hydrochloride* was soluble in methanol, sparingly soluble in *iso*propanol, and insoluble in ether, chloroform, or acetone. It separated from methanol–ether in rosettes of microscopic needles, m. p. 174—175° (decomp.) (Found: C, 59·3; H, 5·2; N, 4·2. $C_{16}H_{14}O_2NClS$ requires C, 59·7; H, 5·0; N, 4·4%).

Dithiocarbocarbethoxyglycine (5·0 g.) was heated with benzaldehyde (2·5 g.) and acetic anhydride (10 c.c.) for 3—4 mins. on the steam-bath. Removal of solvents in a vacuum and treatment of the residue with cold methanol yielded a solid. Recrystallised from acetone–water and methanol, *2-carbethoxythio-4-benzylidenethiazol-5-one* (XXI) separated as yellow needles, m. p. 121—123° (yield 16%) (Found: C, 53·5; H, 3·9; N, 4·7. $C_{13}H_{11}O_3NS_2$ requires C, 53·2; H, 3·8; N, 4·8%). Reaction of the thiazolone with hydrogen sulphide in methanolic triethylamine yielded (XVII; R = CO·SH).

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211. *The Kinetics of Aromatic Sulphonation Reactions. Sulphonation by Sulphuric Acid in Nitrobenzene Solution.*

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The sulphonation by sulphuric acid of nitrobenzene itself and of various aromatic compounds in nitrobenzene solution has been studied at a series of temperatures.

The following equation is derived empirically for the rate of reaction:

$$\text{Rate} = \frac{k_1[\text{Ar}][\text{A}]}{(x + x_0)^{1/3}} - \frac{k_2 x[\text{A}]}{1 + \beta x}$$

where [A] = concentration of sulphuric acid, [Ar] = concentration of aromatic compound, x = water formed in the reaction, and k_1, k_2, x_0, and β are constants.

This equation is given a tentative explanation in terms of a mechanism in which $SO_2{\cdot}OH^+$ is the sulphonating agent, and the reverse reaction of hydrolysis is brought about by $Ph{\cdot}NO_2{\cdot}H^+$.

The relation between activation energy, E, and log k_1 is of the form to be expected if the changes in rate from compound to compound are determined almost entirely by changes in E. The halogen compounds (which are of interest in connexion with their anomalous behaviour in orientation) constitute no exception in this respect.

The connexion between changes in E and the dipole moments of the substituent groups is considered. Here again the halogen compounds fall into line with the rest.

There is a rough functional relation between log k_1 and log (k_1/k_2).

PREVIOUS communications from this laboratory have described experiments on the sulphonation of aromatic compounds by sulphur trioxide in nitrobenzene solution (Vicary and Hinshelwood, *J.*, 1939, 1372; Wadsworth and Hinshelwood, *J.*, 1944, 469; Dresel and Hinshelwood, *ibid.*, p. 649). The present work extends the study to sulphonation by sulphuric acid in the same medium.

The chief experimental difficulty lies in the fact that the rate of sulphonation slows down very markedly as water is formed in the reaction which, therefore, can be followed conveniently only in its initial stages. To do this by the obvious method of titration with alkali is inaccurate since there are, in the circumstances, only small changes in a large acid titre. The difficulty was overcome as follows. 100% Sulphuric acid is completely miscible with nitrobenzene, but the addition of a few per cent. of water causes turbidity. If the phase relations of the ternary system nitrobenzene–water–sulphuric acid have been established, then, for any given

$Ph{\cdot}NO_2 : H_2SO_4$ ratio, the amount of water at the turbidity point is known. If a mixture of nitrobenzene and 100% sulphuric acid is titrated with another mixture containing nitrobenzene and, say, 95% sulphuric acid, a definite titre of the latter will bring the system to the turbidity point. If now the mixture of nitrobenzene and 100% sulphuric acid is allowed to react for some time so that a small quantity of water is formed, and if the final mixture is titrated again with the 95% acid, the titre will be less than before, and from the change the amount of water present before titration can be calculated. By suitable choice of the concentration of acid in the titrating solution, the titre can be magnified to any required degree so that we have available a micro-method for the direct estimation of the water formed.

The method has proved very satisfactory provided that suitable calibrations are made, separate ones being naturally required for each concentration of each aromatic compound employed.

In the first experiments nitrobenzene itself was both solvent and reactant. Its rate of sulphonation is so much slower than that of many other aromatic compounds that it can be used as a solvent for them in other experiments. If necessary, a small correction for the sulphonation of the solvent can be applied, but it is usually negligible.

The rate of sulphonation is dependent upon the precise water content of the sulphuric acid, and this has to be controlled very carefully. The method of thermal analysis proved extremely convenient for this purpose.

The rate of reaction proves to be proportional to the total sulphuric acid concentration, [A], and the concentration of the aromatic compound [Ar]. Thus the *initial* rate of reaction, in the absence of added water, is given by k[Ar][A]. Over the range studied [Ar] and [A] scarcely change during the sulphonation. Nevertheless, the rate, and therefore k, drops very steeply as reaction proceeds. An example is shown in Figs. 3 and 4. The drop is due to two separate causes. On the one hand, the rate of the forward reaction itself falls as water is formed, and, on the other hand, a back reaction soon sets in. The two effects were disentangled by making measurements on the initial rate of reaction with varying quantities of added water, and comparing their effect with that of corresponding amounts of water formed by reaction. Figs. 5 and 6 show examples of the comparison. The upper curves give the effect of added water, the lower that of water formed in the sulphonation. The difference provides a measure of the reverse reaction, the existence of which was also proved by direct experiment. Every compound examined gave results of the general form shown in Figs. 5, 6, and 8.

These results can be expressed in the following way:

$$\text{Rate of sulphonation} = k[\text{Ar}][\text{A}] = \frac{k_1[\text{Ar}][\text{A}]}{\{x + (k_1/k_0)^3\}^{1/3}} - \frac{k_2 x[\text{A}]}{(1 + \beta x)}$$

or so long as [Ar] and [A] remain constant

$$k = \frac{k_1}{\{x + (k_1/k_0)^3\}^{1/3}} - \frac{k_2' x}{(1 + \beta x)}$$

where x is the amount of water formed in the reaction; k_1/k_0 is the same for all the compounds.

These expressions represent the rates empirically, so that the ratio of k_1/k_2 will be proportional to, though not equal to, the equilibrium constant.

With certain approximations about the equilibria prevailing in the nitrobenzene solutions, these equations may be given a tentative theoretical interpretation. They appear in fact to be consistent with the hypothesis that the sulphonating agent is the ion $SO_2{\cdot}OH^+$, that this expels a proton from the aromatic compound, the proton being taken up by the nitrobenzene to form $Ph{\cdot}NO_2{\cdot}H^+$, and that, in accordance with the principle of detailed balancing, the reverse reaction is caused by the attack on the sulphonic acid, not of the ion H_3O^+ but of $Ph{\cdot}NO_2H^+$; *e.g.*,

$$C_6H_6 + SO_2{\cdot}OH^+ + Ph{\cdot}NO_2 \rightleftharpoons C_6H_5{\cdot}SO_2{\cdot}OH + Ph{\cdot}NO_2H^+$$

This view is consistent with the preparative experience that increasing water content hinders both sulphonation *and* hydrolysis of the sulphonic acid. The principal object of the experiments was to obtain information about the influence of substituents on the activation energy so that this incidental conclusion is given with due reserve, since other mechanisms might conceivably be made also to fit.

Experimental.

Materials.—Nitrobenzene was purified by distillation and then by four successive recrystallisations in which it was frozen and re-melted with rejection of the first portions of the melt. The other aromatic compounds were distilled and crystallised to constant b. p. or m. p. " Pure " sulphuric acid and oleum

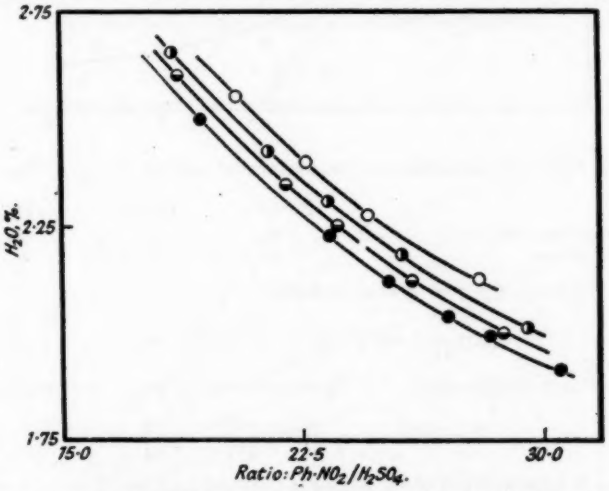
were used in the preparation of the acids, which were standardised as described below. Precautions were taken at all stages to minimise the exposure of materials to moist air.

Standardisation of Sulphuric Acid.—The method was based upon that of Somiya (*Proc. Imp. Acad. Japan*, 1927, **3**, 76). A known quantity of the acid to be tested was run into a standard excess of approximately 10% oleum in a small, covered Dewar vessel provided with a stirrer, and the rise in temperature determined by a thermometer graduated in $\frac{1}{10}$ths. The apparatus was calibrated as follows. From "pure" sulphuric acid, containing a small unknown percentage of water, x, a series of acids were prepared (by weighing) which contained $(x + y)$% of water, y being the percentage of added water. The rise in temperature, $\Delta\theta$, caused in the standard test by each of these was measured. $\Delta\theta$ plotted against the known values of y gave an accurately linear relation, and by extrapolation to $\Delta\theta = 0$, x could be found. $\Delta\theta$ was independent of the strength of the oleum used in the test and no temperature change occurred when two samples of oleum of different strengths were mixed. The knowledge of x for the "pure" sulphuric acid allowed the preparation from it of any required acid, the final strength always being tested by the direct thermometric method.

Phase Relations of the Reactants.—The ternary system nitrobenzene–sulphuric acid–water was studied by Bailey and Hilton (*J.*, 1936, 1571), but for our present purpose more detailed investigation over special ranges was needed. Curves of the type shown in Fig. 1 were plotted for each set of conditions

FIG. 1.

Ternary system: $C_6H_5{\cdot}NO_2$–H_2SO_4–H_2O *with small additions of* C_6H_6.



Successive curves correspond to $[C_6H_6] = 0{\cdot}1404$, $0{\cdot}273$, $0{\cdot}411$ *and* $0{\cdot}542$ *molar, respectively.*

to be employed. A volume of nitrobenzene (32·0 c.c.) was placed in a stoppered tube, a certain quantity of the aromatic compound under investigation added if necessary, and the appropriate quantity of approximately 100% sulphuric acid added (exact water content known). The mixture was titrated with 96% sulphuric acid (also in nitrobenzene but in a different proportion) until it was just turbid. From the weights and compositions of the solutions the total water content at this point could be calculated, and expressed as a percentage of the total acid. The addition of the small amounts of benzene and other reactants in fact made relatively little difference to the results though they were always allowed for.

To obviate any error that may have been due to an initial rapid reaction between sulphuric acid and the aromatic compound before titration, the system was sometimes titrated half way to turbidity before the addition of the 100% acid. At this stage there was enough water present to make reaction quite negligibly slow. It was found, however, that this procedure gave the same titre as when the acid was added before any partial titration. Thus the usual method was to add the aromatic reagent, then the acid, and to titrate immediately.

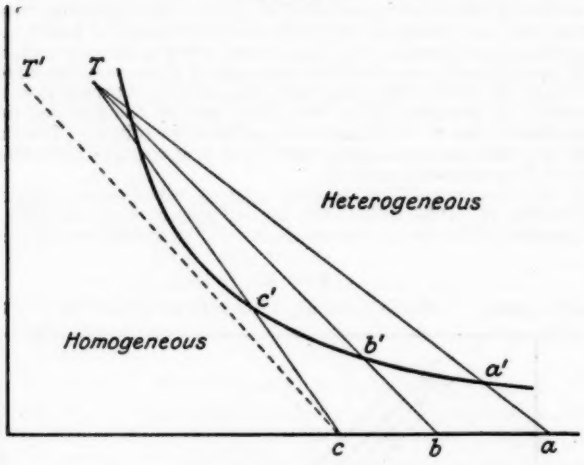
In connexion with the choice of the titrating solution there arises a point which is explained by Fig. 2; a, b, and c are the compositions of the initial mixture, T that of the titrating acid. End-points are reached at a', b', and c', but with an acid T' no end-point would be reached with c. Hence T must be chosen so as to lie close to the equilibrium line. In other words, the titrating solution must be only just clear. Compositions much to the left of c cannot be employed. This restricts somewhat the range over which the initial acid concentration can be varied in the reaction velocity experiments.

The form of the ternary diagrams obtained with any given specimen of nitrobenzene provides a criterion of its quality. If the solvent contains water the curve becomes steeper. Measurements made with nitrobenzene after successive crystallisations showed that there was no appreciable change in the slope after the fourth, and for this reason all samples were recrystallised four times before use. A separate ternary diagram was determined for each sample of solvent and for each concentration of each aromatic compound, whenever possible on the same day as the reaction measurements.

Reaction Velocity Measurements.—Measurements were made in stoppered tubes in thermostats

(±0·02°). Typical quantities employed were: nitrobenzene 32·0 c.c.; sulphuric acid 0·2268M; aromatic compound 0·08—1·0M. The composition in respect of all components except reaction products could be taken as nearly constant during the reaction. The samples were titrated from a micro-burette

FIG. 2.



at suitable intervals of time, and the amount of water formed was calculated. The calculation is carried out as follows :

	$Ph{\cdot}NO_2$.	H_2SO_4.	H_2O.
From reaction mixture	ϕ_1	S_1	w_1
From titration	$\phi_2 = \alpha T$	$S_2 = \beta T$	$w_2 = \gamma T$

where T = titre in g. and $\alpha + \beta + \gamma = 1$, and are known.

$$\text{Ratio at end point} = \frac{\phi_1 + \phi_2}{S_1 + S_2} = R$$

A curve of R against P is available where P = % of water in the acid. P is read off.

Now
$$P = 100\left[\frac{(w_1 + \gamma T)}{(S_1 + \beta T) + (w_1 + \gamma T)}\right]$$

whence w_1 is known. A typical set of observations is recorded in Table I.

TABLE I.

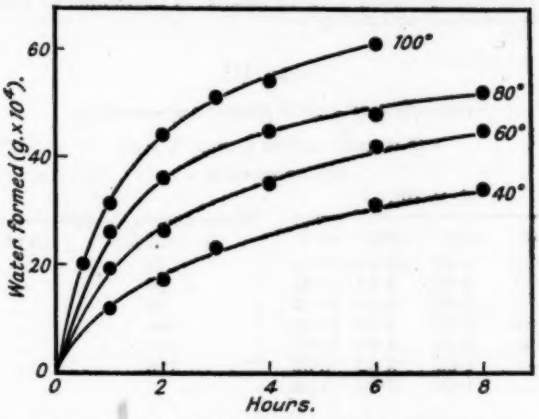
Example of determination of points on a reaction–time curve.

Titrating solution : Nitrobenzene = 141·277 g. Strength of acid = 96·30%. Sulphuric acid = 19·496 g. Density of solution = 1·258. $\alpha = 0{\cdot}8788$; $\beta = 0{\cdot}1167$; $\gamma = 0{\cdot}0045$.
m-Xylene, 15° : [*m*-Xylene] = 0·099M = 0·40 c.c. [Acid] = 0·2268M = 0·40 c.c. $Ph{\cdot}NO_2$ = 32·0 c.c.

Time, hrs.	Titre, c.c.	Nitrobenzene, $(\phi_1 + \alpha T)$ g.	Sulphuric acid, $(S_1 + \beta T)$ g.	Ratio $R = \frac{\phi_1 + \alpha T}{S_1 + \beta T}$.	P%, from ternary diagram.	Water formed (g. × 10^4) per reaction tube.
0	6·46	45·69	1·6802	27·20	2·145	0·0
½	6·27	45·43	1·6525	27·52	2·132	6·1
1	5·86	45·03	1·5923	28·28	2·103	11·1
3	5·44	44·57	1·5308	29·12	2·076	20·5
5	4·88	43·95	1·4486	30·34	2·042	26·8
8	4·44	43·46	1·3841	31·40	2·018	33·3
10	4·12	43·11	1·3371	32·24	2·000	39·0

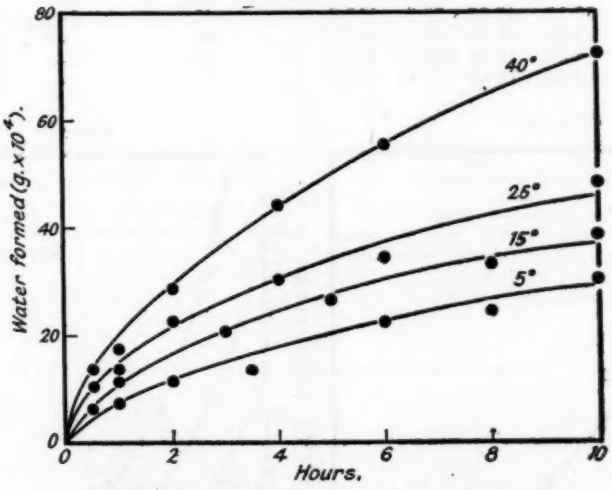
The calculation of velocity constants was carried out by drawing tangents to reaction–time curves, such as those shown in Fig. 3. The rate was first expressed in the form : g. of water formed per hour.
But rate = kc_1c_2, where c_1 and c_2 are the (practically steady) concentrations of acid and aromatic compound respectively, and from this relation k was expressed in g.-mol./L-sec. units.
Influence of Concentration of Acid and of Aromatic Compound.—The influence of the concentration of the sulphuric acid is shown in Table II(a). The reaction is of the first order with respect to $[H_2SO_4]$.
The influence of the concentration of aromatic compound is shown in Table II(b). The reaction is of the first order with respect to the aromatic compound.

FIG. 3*a*.



Sulphonation of nitrobenzene at various temperatures.

FIG. 3*b*.



Sulphonation of m-*xylene at various temperatures.*

TABLE II.

(a) *Order of reaction with respect to the sulphuric acid concentration.*

Compound.	Sulphuric acid concn., g.-mols. per l.	Initial reaction rate × 10^7, g.-mols./l./sec.	Ratio.	Compound.	Sulphuric acid concn., g.-mols. per l.	Initial reaction rate × 10^7, g.-mols./l./sec.	Ratio.
Benzene	0·170	7·00	41·1	Chlorobenzene	0·168	1·83	10·9
	0·227	9·31	41·0		0·258	2·76	10·7
	0·281	12·00	42·6		0·336	3·88	11·5

(b) *Order of reaction with respect to the aromatic reagent concentration.*

Compound.	Concn., g.-mols. per l.	Initial reaction rate × 10^7, g.-mols./l./sec.	Ratio.	Compound.	Concn., g.-mols. per l.	Initial reaction rate × 10^7, g.-mols./l./sec.	Ratio.
Benzene	0·140	4·70	33·6	Chlorobenzene	0·120	1·47	(12·3)
	0·273	9·75	35·7		0·236	2·22	9·4
	0·411	12·00	29·2		0·350	3·17	9·1
	0·542	15·90	29·4		0·462	4·00	8·7

Variation of k *during the Course of the Reaction.*—The rate is given by k[Ar][A] and drops rapidly as the reaction proceeds. The corresponding drop in [Ar][A] is negligible, so that k itself must change. Typical results are given in Table III and in Fig. 4.

TABLE III.

Variation of k *with progress of reaction.*

(k is measured in g.-mol./l. sec.)

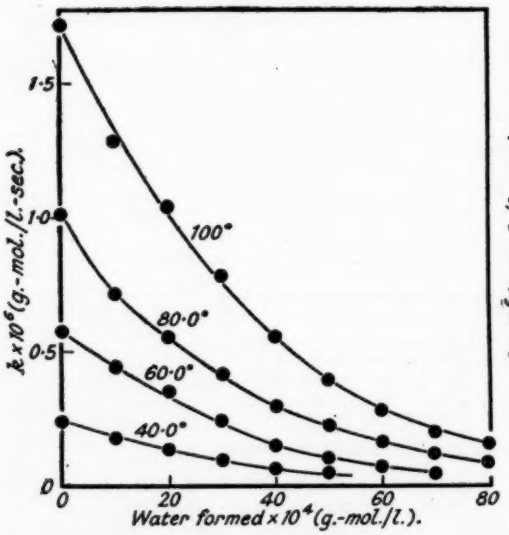
Chlorobenzene.

Water concn. × 10^4 (g.-mol./l.).	$k \times 10^6$. 15·0°.	25·0°.	40·0°.	60·0°.	Water concn. × 10^4 (g.-mol./l.).	$k \times 10^6$. 15·0°.	25·0°.	40·0°.	60·0°.
0	2·65	4·88	10·62	22·96	70	—	—	2·83	5·96
10	2·11	4·07	8·49	18·91	80	—	—	2·33	5·30
20	1·69	3·42	6·39	15·10	90	—	—	2·04	4·87
30	1·34	2·75	4·93	12·30	100	—	—	—	4·45
40	0·98	2·19	4·08	10·07	110	—	—	—	3·76
50	—	1·65	3·82	8·52	120	—	—	—	3·33
60	—	1·19	3·25	7·24					

m-Xylene.

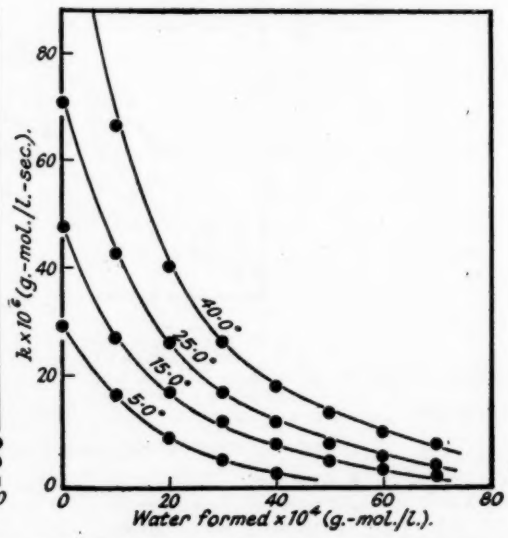
Water concn. × 10^4 (g.-mol./l.).	$k \times 10^6$. 5·0°.	15·0°.	25·0°.	40·0°.	Water concn. × 10^4 (g.-mol./l.).	$k \times 10^6$. 5·0°.	15·0°.	25·0°.	40·0°.
0	29·18	47·95	70·9	116·8	40	2·08	7·51	11·47	18·35
10	16·68	27·10	42·75	66·71	50	—	4·80	7·51	13·55
20	8·55	17·10	26·27	40·65	60	—	3·13	5·21	10·00
30	4·59	11·47	17·10	26·48	70	—	2·08	4·17	7·92

FIG. 4*a*.



Sulphonation of nitrobenzene at various temperatures.

FIG. 4*b*.



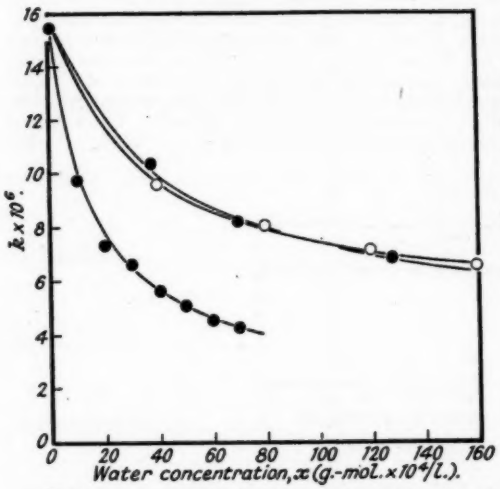
Sulphonation of m*-xylene at various temperatures.*

Influence of Initially Added Water on the Initial Rate.—For several compounds the initial rate was determined in experiments with a range of acids made up to contain small known percentages of water. The initial rate falls with the water content (Figs. 5 and 6). These figures also show lines calculated from the formula $k = k_1/(x + x_0)^{1/3}$ where x is the amount of water initially added and x_0 is a constant, which proves to be nearly independent of the aromatic compound used (and according to a possible theory should be completely independent). The form of this relation is discussed later. In the meantime the figures show that it is a satisfactory empirical representation of the results. Experimental values found for k_1/k_0 were: benzene 0·109, *m*-dichlorobenzene 0·135, toluene 0·1007, α-nitronaphthalene 0·1114, naphthalene 0·0844. It is assumed therefore that where the experimental value has not been directly determined a mean value may be used for all the aromatic compounds studied. In contrast with the nearly constant effect of added water on the initial rate, the variation in rate with water formed in the reaction is very specific and different for each aromatic compound, as is shown by the selection of curves

in Fig. 7. **Thus part at least of the effect of the water formed in reaction is due to the setting up of a reverse change.**

FIG. 5.

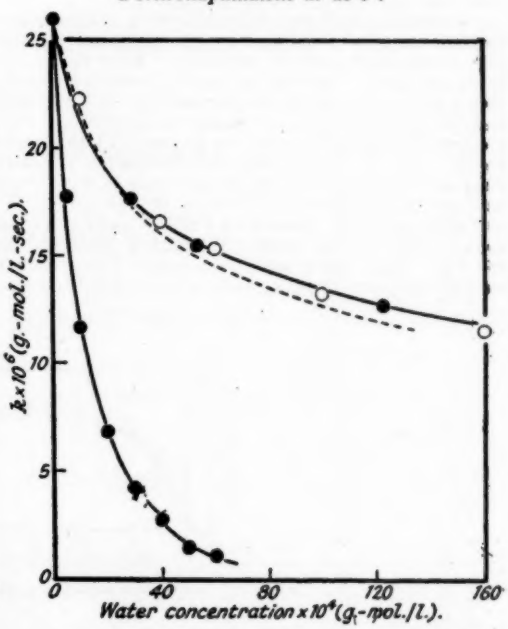
Benzene at 40·0°.



Upper curves: full circles, experimentally found influence of added *water on initial value of* k; *open circles, calculated from* $k = k_1/[x + (0{\cdot}109)^3]^{1/3}$, *where* $k_1 = 15{\cdot}4 \times 10^{-6}$. *Lower curve: influence of water formed in reaction on* k.

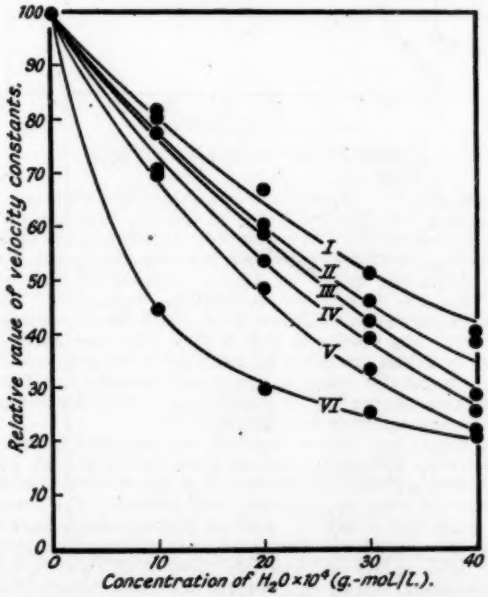
FIG. 6.

α-Nitronaphthalene at 40·0°.



Lower curve: influence of water formed in reaction on k. *Upper curves: full circles, experimental; open circles, calculated from* $k = k_1[x + (0{\cdot}1114)^3]^{1/3}$ *with* $k_1 = 2{\cdot}98 \times 10^{-6}$; *broken line, calculated with* $k_1/k_0 = 0{\cdot}108$ (*average value*).

FIG. 7.

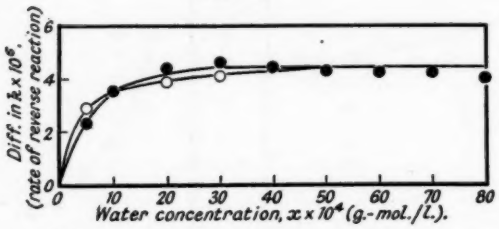


k *as a function of water formed.* (*I*) PhBr. (*II*) PhCl. (*III*) PhMe. (*IV*) $Ph{\cdot}NO_2$. (*V*) $C_6H_4(NO_2)Me$. (*VI*) m-$C_6H_4Cl_2$.

Influence of Reaction Products. Reverse Reaction.—A comparison of the pairs of curves in Figs. 5 and 6 shows that initially added water has less effect than a corresponding amount formed by reaction. This provides further evidence that the setting in of a reverse reaction contributes to the diminution of the gross reaction rate, as measured by k. The existence of the reverse reaction was confirmed in the following way.

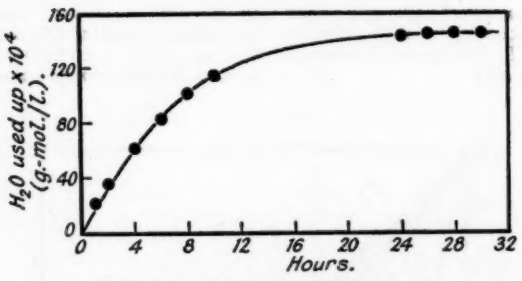
A reaction mixture of the following composition was weighed into a flask: nitrobenzene, 200 c.c.; sulphuric acid of 95·26% strength, 1·8965 g.; sodium benzenesulphonate, 0·6056 g. The salt was 88·0% pure (remainder sodium chloride). Thus the mixture was 0·0248M in water and 0·0147M in benzenesulphonic acid. The turbid reaction mixture was shaken, and a 10 c.c. portion titrated until clear with 100% sulphuric acid in nitrobenzene (1 : 80), the titre being 8·48 c.c. The remainder was kept at 25·0°, and 10 c.c. portions were titrated at intervals. From the gradual drop in titre occurring as water was used up in the hydrolysis the progress of this reaction could be followed. The results are shown in Fig. 9. For the calculations the titre had to be calibrated against water content of the reaction mixture. Suppose that y g. of water are removed to form $98y/18$ g. of H_2SO_4; the amounts of H_2SO_4 and of H_2O now present are $0{\cdot}9526 \times 1{\cdot}897 + 98y/18$ and $0{\cdot}047 \times 1{\cdot}897 - y$, respectively, that is, the total weight of "sulphuric acid" present is $1{\cdot}897 + 4{\cdot}44y$ and its percentage strength is expressible in terms of y. For the calibration experiment a titration is made with an acid somewhat stronger than the original, namely, 96·07%. This would have been formed by an amount of reaction such that $y = 0{\cdot}01362$. To imitate a reaction mixture for which this value of y has been reached it is necessary to take $1{\cdot}897 + (0{\cdot}01362 \times 4{\cdot}44)$

FIG. 8.



Reverse reaction with benzene at 40·0°.

FIG. 9.



Hydrolysis of benzenesulphonic acid.

$= 1{\cdot}958$ g. of the 96·07% acid and the appropriate amount of the sodium benzenesulphonate, that is, 0·6056 g. less the amount reacting with the 0·01362 g. of water. Allowing for the purity of the salt, we find the amount required to be 0·4501 g. The mixture is therefore made up to contain: nitrobenzene, 200 c.c.; sulphuric acid (96·07%), 1·9660 g.; sodium benzenesulphonate, 0·45 g. This is 0·0214M in water and 0·0111M in the sulphonic acid. A 10 c.c. portion of this required 6·68 c.c. of the 100% titrating solution. Thus we have: water, 0·0248M, titre, 8·48: water, 0·214M, titre, 6·68. From calibrations of this kind a curve can be drawn from which the concentration of water at any stage of the reaction can be read off. The results in Fig. 9 show that the water concentration dropped by 0·0145 g.-mol./l. If the hydrolysis had proceeded to completion the drop would have been 0·0147, so that in the conditions of the experiment the reaction was nearly complete. The conditions are not quite comparable with those prevailing during the sulphonation. Nevertheless the results show that the reverse reaction must be taken very seriously into account.

The principal information about the reverse reaction was obtained indirectly. Its magnitude is in fact given by the difference between two curves such as those shown in Figs. 5 and 6. The result, which is of similar form in all the examples studied, is illustrated in Fig. 8, where the rate of the reverse reaction is plotted against x, the amount of water or sulphonic acid formed. The result is rather surprising, the contribution to the net rate being, not a term $(-k'x^2)$ as might perhaps have been expected, but one of the form $k_2'x/(1 + \beta x)$. This for the present will be taken as an empirical result, and discussed later.

Since $k_1[\mathrm{Ar}][\mathrm{A}]/(x + x_0)^{1/3}$ does in fact represent the forward rate and $k_2'x/(1 + \beta x)$ the reverse rate, the ratio k_1/k_2' will be proportional to an equilibrium constant, which thus becomes determinable. Results are collected in Table VII.

Temperature Coefficients and Activation Energies.—The values of k (in the expression rate $= k[\mathrm{Ar}][\mathrm{A}]$)

for different values of x were plotted and k_0 determined at four or more different temperatures for each of the compounds studied. The results are recorded in Table IV.

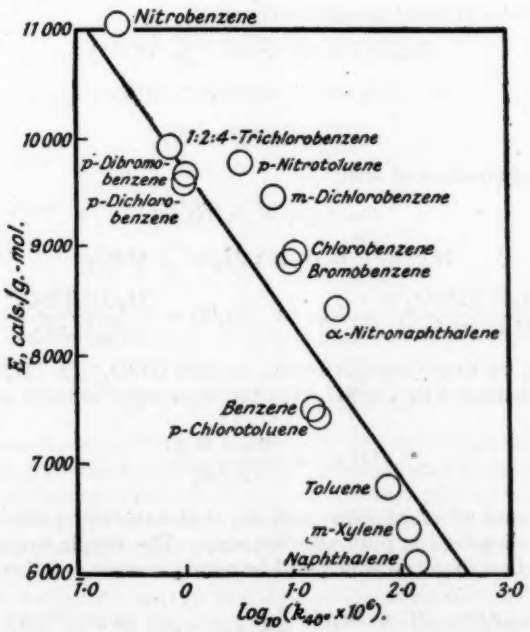
From the plots of ln k_0 against $1/T$ the activation energies were determined by the method of least squares. They are given in Table V, and log k_0 for 40° is plotted against E in Fig. 10. The line is drawn with the slope $-2{\cdot}303RT$.

With nitrobenzene, where the reactant is itself the solvent, the reaction is determined by solvent–solute encounter, and not as in the other examples by solute–solute encounters. The viscosity correction has

TABLE IV.

Compound.	Temp.	$k_0 \times 10^6$.	Compound.	Temp.	$k_0 \times 10^6$.
Benzene	15°	5·1	*p*-Dibromobenzene	25°	0·46
	25	8·0		40	1·01
	40	15·5		60	2·46
	60	30·0		80	5·01
Toluene	15	31·1	*p*-Chlorotoluene	15	5·41
	25	42·7		25	9·32
	40	78·7		40	17·1
	60	151·2		60	33·3
m-Xylene	5	29·2	1 : 2 : 4-Trichlorobenzene	25	0·34
	15	48·0		40	0·73
	25	70·9		60	1·95
	40	116·8		80	4·23
Chlorobenzene	15	2·65	Nitrobenzene	40	0·24
	25	4·88		60	0·57
	40	10·6		80	1·01
	60	23·0		100	1·72
Bromobenzene	15	3·01	*p*-Nitrotoluene	25	1·50
	25	4·42		40	3·26
	40	9·55		60	7·95
	60	24·4		80	19·6
m-Dichlorobenzene	25	2·51	Naphthalene	5	40·0
	40	6·70		15	61·2
	60	15·6		25	82·4
	80	35·2		40	141·3
p-Dichlorobenzene	25	0·49	α-Nitronaphthalene	15	7·76
	40	0·98		25	13·1
	60	2·26		40	26·1
	80	5·34		60	57·2

FIG. 10.



Activation energy and log (rate).

TABLE V.

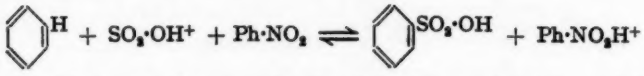
Compound.	$k_0 \times 10^6$ at 40°.	E.	Compound.	$k_0 \times 10^6$ at 40°.	E.
Naphthalene	141·3	6,100	Bromobenzene	9·5	8,850
m-Xylene	116·7	6,400	*m*-Dichlorobenzene	6·7	9,460
Toluene	78·7	6,790	*p*-Nitrotoluene	3·3	9,770
α-Nitronaphthalene	26·1	8,430	*p*-Dichlorobenzene	0·98	9,570
p-Chlorotoluene	17·1	7,440	*p*-Dibromobenzene	1·01	9,670
Benzene	15·5	7,500	1 : 2 : 4-Trichlorobenzene	0·73	9,940
Chlorobenzene	10·6	8,940	Nitrobenzene	0·24	11,060

therefore been applied (Moelwyn-Hughes, "Kinetics of Reactions in Solution", 1st Ed., p. 158). The value of Q in the equation $\frac{d \ln (1/\eta)}{dT} = \frac{Q}{RT^2}$ is 3000 cals., and this has been added to the observed activation energy to correct for the effect of diminution in encounter numbers as the temperature rises.

DISCUSSION.

(a) *Kinetics of Forward and Reverse Reactions.*—The possible equilibria in the system sulphuric acid–nitrobenzene–water are rather complex, and the complete treatment of the system is difficult. The kinetic relationships are, however, of a distinctive form, and an approximate interpretation seems possible in the following way, though, in view of the assumptions and approximations which have to be made, the treatment must be regarded as tentative.

The hydrolysis of the sulphonic acid is not promoted by water in a way which admits H_3O^+ as the attacking agent (Fig. 8). It proves more satisfactory to assume $Ph{\cdot}NO_2{\cdot}H^+$. If this hypothesis is adopted, it follows from the principle of detailed balancing that $SO_3{\cdot}OH^+$ would probably be the active agent in the sulphonation, thus:



The consequences of this assumption may be developed approximately as follows:

$$2H_2SO_4 \rightleftharpoons SO_3{\cdot}OH^+ + HSO_4^- + H_2O$$

$$\frac{[SO_3{\cdot}OH^+][HSO_4^-][H_2O]}{[H_2SO_4]^2} = K_1$$

The ionisation may be taken to be small, the conductivity of sulphuric acid in nitrobenzene being low, and if the water content is sufficiently small

$$[H_2SO_4] \gg [SO_3{\cdot}OH^+] \gg [H_3O^+]$$

Also $$[SO_3{\cdot}OH^+] \sim [HSO_4^-] = f$$

Therefore $$f^2[H_2O]/[A]^2 = K_1$$

where [A] = total concentration of acid.

$$f = [A]\sqrt{K_1}/\sqrt{[H_2O]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

If $$H_2SO_4 + H_2O \rightleftharpoons H_3O^+ + HSO_4^-$$

$$\frac{[H_3O^+][HSO_4^-]}{[H_2O][H_2SO_4]} = K_2 \quad \text{or} \quad [H_2O] = \frac{[H_3O^+][HSO_4^-]}{K_2[H_2SO_4]}$$

Now the water content, by hypothesis, is small; so that $[HSO_4^-] \gg [H_3O^+]$ (remembering that much of the HSO_4^- is balanced by $Ph{\cdot}NO_2{\cdot}H^+$), but such water as there is will be predominantly in the form H_3O^+ and

$$[H_2O] \sim \frac{(W + W_0)f}{K_2[A]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

W being any small amount of *added* water and W_0 that naturally present in equilibrium when 100% sulphuric acid is dissolved in pure nitrobenzene. The simple summation of $(W + W_0)$ is of course an approximation, but one which will be nearly correct. Substituting for $[H_2O]$ from (1), we have

$$\frac{K_1[A]^2}{f^2} \sim \frac{(W + W_0)f}{K_2[A]} \quad \text{whence} \quad f = \frac{(K_1K_2)^{1/3}[A]}{(W + W_0)^{1/3}}$$

Now in excess of $Ph{\cdot}NO_2$ the rate of the forward reaction will be proportional to [Ar]f, and thus, for *small* water contents, we shall have

$$\text{Forward rate} = \frac{k_1[\text{Ar}][\text{A}]}{(W + W_0)^{1/3}}$$

or, if the water is all formed in the reaction, $W = x$, so that

$$\text{Forward rate} = \frac{k_1[\text{Ar}][\text{A}]}{(x + x_0)^{1/3}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where x_0 has the same meaning as W_0.

This, as has been shown, expresses the results adequately. At higher water contents it must cease to apply.

For the reverse reaction the important quantity is $[Ph{\cdot}NO_2H^+]$. The magnitude of this, over certain ranges, will be principally determined by the competition

$$Ph{\cdot}NO_2 + H_2SO_4 = Ph{\cdot}NO_2H^+ + HSO_4^-$$

$$H_2O + H_2SO_4 = H_3O^+ + HSO_4^-$$

If $$[H_2SO_4] \sim [\text{A}],\ [H_3O^+] \sim (W + W_0) \sim W'$$

$$[Ph{\cdot}NO_2] = [\text{S}]$$

then $$[Ph{\cdot}NO_2H^+] = \frac{K_3[\text{S}][\text{A}]}{[HSO_4^-]}$$

but $$[H_3O^+] + [Ph{\cdot}NO_2H^+] = [HSO_4^-]$$

$$[Ph{\cdot}NO_2H^+] = \frac{K_3[\text{S}][\text{A}]}{W' + [Ph{\cdot}NO_2H^+]}$$

$$[Ph{\cdot}NO_2H^+] = \tfrac{1}{2}\left[- W' + W'\left(1 + \frac{4K_3[\text{S}][\text{A}]}{W'^2}\right)^{1/2}\right]$$

and if the second term in the bracket is small this becomes approximately

$$[Ph{\cdot}NO_2H^+] \sim K_3[\text{S}][\text{A}]/W'$$

Now the rate of the back reaction will be proportional to [sulphonic acid][$Ph{\cdot}NO_2H^+$] and thus

$$\text{Back rate} = \text{const.}\ \frac{x[\text{S}][\text{A}]}{W'} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Combining (3) and (4) and putting $W' = W + W_0 = x + x_0$ when no water is added initially ($x_0 \equiv W_0$)

$$\text{Net rate} = k[\text{Ar}][\text{A}] = \frac{k_1[\text{Ar}][\text{A}]}{(x + x_0)^{1/3}} - \frac{k''x[\text{A}]}{(x + x_0)}$$

When $x = 0$, $k = k_0$, so that $k_0 = k_1/(W_0)^{1/3}$

$$k = \frac{k_1}{\{x + (k_1/k_0)^3\}^{1/3}} - \frac{k_2x}{[\text{Ar}](1 + \beta x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad (5a)$$

where k_2 and β are new constants.

Since [Ar] does not change appreciably, this becomes

$$k = \frac{k_1}{\{x + (k_1/k_0)^3\}^{1/3}} - \frac{k_2'x}{(1 + \beta x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5b)$$

This equation, as has been shown, gives a fair account of the experimental results.

It is recognised that the above contains many approximations but may be regarded as a preliminary interpretation of the general form of the experimental results. The approximations are such that the expression for the forward reaction will be best at lower water contents, and that for the reverse reaction at the higher water contents. In any event as an empirical equation (5*b*) is satisfactory. k_1/k_2 is therefore used as a measure of an equilibrium constant.

(b) *Relation between Activation Energy and Rate.*—The summarised results of Table V are plotted in Fig. 10, which shows that the changes in E due to the substituents play the principal part in determining the changes in reaction rate. If they played the sole part the points would

lie on a line of slope $-2{\cdot}303RT$. Such a line is shown in the figure, and, it is evident that, having regard to the large scale of the plot, the points do not lie far from it. However, all the points in the upper half of the diagram lie on or to the right of the line, while all those in the lower half lie to the left. Thus the best line would be a little steeper than that drawn; that is, the rate does not decrease as rapidly as would be expected simply from the changes of activation energy. In other words the well-known compensation of the energy and entropy factors is in evidence, but only to a small extent.

The next matter of interest is that the point for nitrobenzene lies just as expected in relation to the others. E for nitrobenzene involved the "viscosity" correction of 3000 calories. If this had not been applied the point would lie in a completely inconsistent relation to the others. Thus the coherence of the results vindicates the application of the correction. It may be noted that the addition of the corresponding correction to the results of Dresel and Hinshelwood (*loc. cit.*), which was not done, would correspondingly improve their coherence.

FIG. 11.

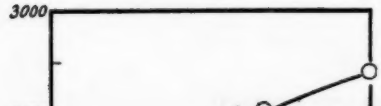
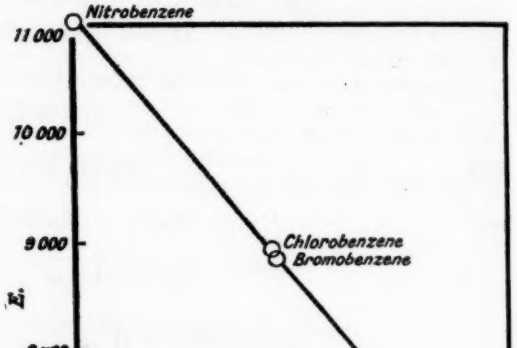


FIG. 12.



Activation energy and dipole moment.

The points for the seven halogen derivatives lie in a coherent relation to the others. As is well known, the behaviour of halogens as directing groups is anomalous in certain respects, but the present results confirm those of Dresel and Hinshelwood in indicating that the anomaly does not lie in the nature of the activation energy–entropy of activation relationship.

Fig. 11 shows the effect on E of introducing one, two, and three halogen atoms, or one and two methyl groups respectively into the ring. The tendency to saturation in the effect of the increasing substitution is evident.

(c) *Activation Energy and Dipole Moment.*—In Fig. 12 the values of E for benzene and the monosubstitution products are plotted against the corresponding dipole moments, and a fairly definite fuctional relation is evident. The halogen derivatives appear to fall in line, despite the anomaly referred to above, while toluene deviates somewhat, the effect of methyl groups corresponding to a value of μ rather greater than the actual one.

That the relation of E and μ for chloro- and bromo-benzene should be normal is interesting in view of the current interpretation of the orientating influence of halogens. They are deactivating, as is to be inferred from the moments, but *o*- and *p*-directing in a way which shows reaction to depend upon a tautomeric change provoked by the attacking agent. This change involves a temporary reversal of the natural moment, and requires the expenditure of work. The present result shows that the amount of this work is adjusted to the moment which has to be reversed.

In Table VI are given the actual moments of the various compounds together with the effective moments of the poly-substitution products, that is, the value of μ corresponding,

TABLE VI.

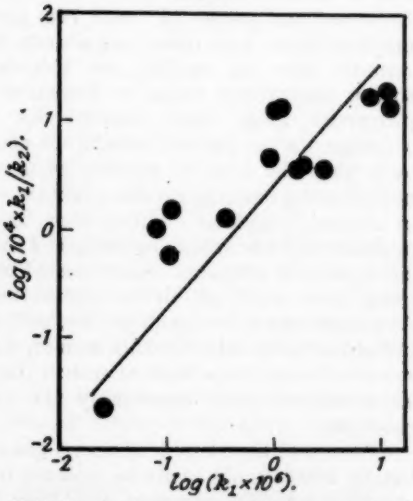
Activation energy and dipole moment.

Compound.	*E*.	Experimental μ.	Effective μ.
Toluene	6,790	+0·41	—
Benzene	7,500	0	—
Chlorobenzene	8,940	−1·56	—
Bromobenzene	8,850	−1·53	—
Nitrobenzene	11,060	−3·97	—
Naphthalene	6,100	—	+1·60
m-Xylene	6,400	—	+1·26
α-Nitronaphthalene	8,430	—	−1·04
p-Chlorotoluene	7,440	—	+0·10
m-Dichlorobenzene	9,460	—	−2·17
p-Nitrotoluene	9,770	—	−2·53
p-Dichlorobenzene	9,570	—	−2·33
p-Dibromobenzene	9,670	—	−2·40
1 : 2 : 4-Trichlorobenzene	9,940	—	−2·70

according to the line in Fig. 12, to the observed values of *E*. In the *p*-dihalogen derivatives the effective moment would not be expected to bear any relation to the observed moment since in the former there must be some degree of reinforcement and in the latter there is complete cancellation of the separate effects of the two atoms. Actually the effective moment of the di-derivatives is considerably less than $2\mu_{mono}$, and of the tri-derivative much less than $3\mu_{mono}$.

The effective moment of xylene is greater than twice the observed value for toluene (though it is less than twice the effective value for toluene). Naphthalene has a high effective moment, nearly 4 times the observed value for toluene. The activating effect of hydrocarbon substituents is uniformly greater than would be inferred from $\mu_{toluene}$. This same influence is in evidence with nitronaphthalene, nitrotoluene, and chlorotoluene, where the contribution of the hydrocarbon substituent in opposing the deactivating effect of Cl or NO_2 is far greater than would be expected from the measured dipole moments of monoalkyl compounds.

FIG. 13.



Velocity constant and equilibrium constant.

(d) *Relation of* k_1 *and* K.—In Table VII are collected the values of the principal constants. Most of them have already been discussed. One further matter remains. The ratio k_1/k_2, according to the theory given above, should be proportional to an equilibrium constant, *K*, and it is of interest

TABLE VII.

Compound.	k_1/k_0.	$k_1 \times 10^6$.	$k_2 \times 10^6$.	$\beta \times 10^{-3}$.	$10^4 k_1/k_2$.
Naphthalene	0·084	11·41	5·636	1·444	20·24
m-Xylene	—	12·38	8·794	1·615	14·08
Toluene	0·101	7·952	4·666	0·947	17·04
α-Nitronaphthalene	0·111	2·978	8·168	3·572	3·647
p-Chlorotoluene	—	1·847	4·586	3·357	4·026
Benzene	0·109	1·682	4·634	3·890	3·629
Chlorobenzene	—	1·145	0·850	1·049	13·41
Bromobenzene	—	1·037	0·816	1·050	12·71
m-Dichlorobenzene	0·135	0·919	1·992	2·357	4·613
p-Nitrotoluene	—	0·350	2·749	1·110	1·274
p-Dichlorobenzene	—	0·106	1·715	3·000	0·618
p-Dibromobenzene	—	0·109	0·699	2·214	1·561
1 : 2 : 4-Trichlorobenzene	—	0·079	0·769	3·625	1·028
Nitrobenzene	—	0·0255	11·31	1·530	0·0225

(Where k_1/k_0 was not determined experimentally the mean value was taken, namely, 0·108.)

to see whether there is any sign of the well-known logarithmic correlation between rate constant and equilibrium constant. Accordingly, log k_1 has been plotted against log (k_1/k_2) in Fig. 13, and it appears that there is a general correlation in the sense to be expected, though no accurate relationship seems to exist.

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212. *Substitution Reactions of Triphenylethylene and its Derivatives. A Contribution to the Problem of Synthetic Analogues of Progesterone.*

By NG. PH. BUU-HOÏ and RENÉ ROYER.

In the course of an investigation on the synthesis of compounds which may exhibit progestational activity, the chemistry of triphenylethylene has been explored. From this hydrocarbon and from 1 : 2-diphenyl-1-*p*-chlorophenylethylene, monoketones were readily obtained, and the acyl group in these compounds is shown to be located in the 2-phenyl nucleus. Other reactions leading to amino- and to nitro-derivatives of triphenylethylene and some of its halogenated derivatives are also described. The physiological properties of the new compounds are mentioned and discussed.

DURING the last five years, numerous attempts have been made to build synthetic substances having progestational activity by introducing the characteristic acetyl group of progesterone into a molecule which would be related to artificial oestrogenic compounds. For instance, Robinson and Jaeger (*J.*, 1941,744) prepared 4-hydroxy-4′-acetyl-αβ-diethyl- and -α-methyl-β-ethyl-stilbene, but these compounds still retained a strong oestrogenic activity; the same remark may be applied to 4′-hydroxy-4-methoxy-3′-acetyl-αβ-diethylstilbene and other similar derivatives made by Brownlee and Duffin (B.P. 550,262), although progesterone-like properties have been claimed for 4-methoxy-4′-acetyl-αβ-diethyldibenzyl. As phenolic substituents are known to enhance oestrogenic properties, Ross (*J.*, 1945, 536) expressed the view that the kind of substances most likely to bear luteal hormone-like activity without perturbating oestrogenic side-effects would be non-phenolic ketones related to stilbene, dibenzyl, or triphenylethylene. This author, however, could not obtain monoketones from any of these or similar hydrocarbons by means of the Friedel–Crafts reaction. In every case, pure products could not be obtained unless acetyl chloride was used in excess, polyacetylated compounds being thus obtained; from triphenylethylene, only a triacetyl compound could be isolated. As progesterone is a monoketone, polyketonic substances would hardly be expected to exhibit luteal hormone activity, and, in fact, these have been found to be inactive. But as there still remained some hope that monoacetylated oestrogenic hydrocarbons would bear some activity, we examined more thoroughly the behaviour of triphenylethylene towards Friedel–Crafts reactions.

We found that 1 mol. of acetyl chloride at 0° gave rather good yields of a mono-substituted ketone which could easily be isolated by vacuum distillation. The crystalline compound thus obtained was homogeneous and may be formulated as 1 : 1-*diphenyl*-2-p-*acetylphenylethylene* (I; X = H, Y = Ac), as substitution on the 1-phenyl nuclei would be expected to produce a mixture of two stereoisomeric compounds. By replacing acetyl chloride with propionyl or *n*-valeryl chloride, the analogous *ketones* (I; X = H, Y = COEt) and (I; X = H, Y = COBu) could similarly be prepared. (From the results of classical work upon substituted derivatives of benzene, the possibility of *o*- and of *m*-substitution can be ignored.)

$CPh_2{:}CX{\cdot}C_6H_4Y$ (*p*) (I.) $\qquad$ $CPh(C_6H_4Cl){:}CX{\cdot}C_6H_4Y$ (II.)

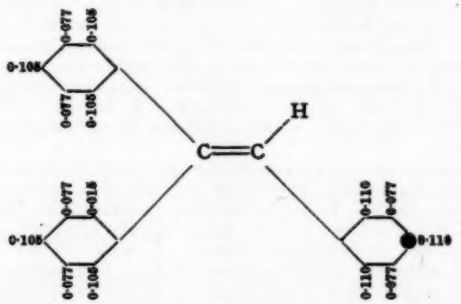
The first two ketones gave crystalline *oximes* which readily underwent Beckmann's transposition into the corresponding 1 : 1-*diphenyl*-2-p-*acylamidophenylethylene* (I; X = H, Y = NHAc or NH·COEt). In view of the potent carcinogenicity of 2-acetamidofluorene (Wilson, Cox, and de Eds, *Cancer Res.*, 1941, **1**, 595) and of several aminostilbenes (Haddow, Harris, and Kon, *Biochem. J.*, 1945, **39**, 2), the first of these derivatives is under test for similar biological properties.

From 1 : 2-*diphenyl*-1-p-*chlorophenylethylene* (II; X = Y = H), prepared by dehydration of the tertiary alcohol obtained from *p*-chlorobenzophenone and benzylmagnesium chloride, a ketone which was probably 1-*phenyl*-1-p-*chlorophenyl*-2-p-*acetylphenylethylene* (II; X = H, Y = COMe) could also be synthesized.

Triphenylethylene and 1 : 2-diphenyl-1-*p*-chlorophenylethylene readily underwent mononitration, and the homogeneous compounds thus obtained may be formulated respectively as 1 : 1-*diphenyl*-2-p-*nitrophenylethylene* (I; X = H, Y = NO_2) and 1-*phenyl*-1-p-*chlorophenyl*-2-p-*nitrophenylethylene* (II; X = H, Y = NO_2).

From the potent oestrogenic and anticarcinogenic 1-bromotriphenylethylene (Y.59) (cf. *Lancet*, 1947, **253**, 172) and from 1-*bromo*-1 : 2-*diphenyl*-2-p-*chlorophenylethylene* (II; X = Br, Y = H), 1-*bromo*-2 : 2-*diphenyl*-1-p-*nitrophenyl*- (I; X = Br, Y = NO_2) and 1-*bromo*-2-*phenyl*-2-p-*chlorophenyl*-1-p-*nitrophenyl-ethylene* (II; X = Br, Y = NO_2) could similarly be prepared, although the presence of bromine rendered the nitration somewhat more difficult.

The fact that substitution of triphenylethylene occurs in the lone phenyl nucleus may be accounted for on the basis of the electronic theory of substitution. The distribution of the density of π-electrons around each atom of carbon in triphenylethylene has been estimated by Daudel *et al.*, by means of the method of " molecular diagrams " based upon mesomerism (Daudel and Pullman, *J. Phys. Radium*, 1946, **59**, 74, 105; Daudel *et al.*, *Rev. Sci.*, 1946, **84**, 489; *Compt. rend.*, 1946, **223**, 947; cf. also Coulson and Daudel, *Rev. Sci.*, 1947, **85**, 29), to be as shown below, from which it will be seen that the " free valency number " of the *p*-carbon atom in the lone phenyl nucleus is definitely greater than that of the corresponding atoms in the other phenyl nuclei.



Physiological Properties.—1 : 1-Diphenyl-2-*p*-acetylphenylethylene and its 1-*p*-chloro-derivative are far more toxic than the parent hydrocarbons, but at the tolerated doses of 20 mg. (in injection), both failed to produce any luteal hormone-like effect in female rabbits. p-*Acetyl-αβ-diethylstilbene*, (*p*)$C_6H_4Ac{\cdot}CEt{:}CEt{\cdot}C_6H_5$, obtained from αβ-diethylstilbene by means of our technique of monoacetylation, proved also to be toxic, as well as completely inactive at the tolerated doses.

Some of the new substances described in this work have been examined for oestrogenic properties. Activities determined upon female spayed rats by means of the Allen–Doisy test are listed below :

Compound.	M.E.D., mg. (single injection).	Compound.	M.E.D., mg. (single injection).
(I; X = H, Y = Ac)	0·1	(I; X = Br, Y = NO_2)	0·1
(I; X = H, Y = COEt)	1	(II; X = Br, Y = H)	5
p-Acetyl-αβ-diethylstilbene	1		

It is noteworthy in this respect that acetylation leaves the activity of triphenylethylene almost unchanged, and that even nitration of 1-bromotriphenylethylene (Y.59) does not suppress its oestrogenic potency.

From consideration of the above-mentioned results, and of the work of Robinson and Jaeger (*loc. cit.*) and of Ross (*loc. cit.*), it appears to be very doubtful whether progesterone-like substances with a sufficient order of potency will ever be found in the field of purely aromatic molecules (see also Dodds, *Chem. and Ind.*, 1947, 373).

Note added June 20th, 1948.—Work by Bergmann, Dimant, and Japhe (*J. Amer. Chem. Soc.*, 1948, **70**, 1618), which appeared while this paper was in the press, suggests that the nitrotriphenylethylene described above might be 1-nitro-1 : 2 : 2-triphenylethylene, since it differs from 1 : 1-diphenyl-2-*p*-nitrophenylethylene synthesised by the Meerwein coupling of *p*-nitrobenzenediazonium salts with ββ-diphenylacrylic acid. This is still in accord with the molecular diagram of triphenylethylene, which also ascribes a high " free valency number " (0·140) to the lone carbon atom.

Experimental.

Acetylation of Triphenylethylene.—The most convenient method of preparing triphenylethylene is the dehydration of diphenylbenzylcarbinol (obtained from benzophenone and benzylmagnesium chloride) by means of anhydrous formic acid or acetyl chloride. An attempt to extend the Gattermann–Skraup synthesis of 2 : 2-diarylethylenes (Gattermann, *Ber.*, 1889, **22**, 1130; Skraup and Nieten, *Ber.*, 1924, **57**, 1300) to phenylacetyl chloride and benzene resulted in formation of only minute quantities of triphenylethylene. A mixture of triphenylethylene (20 g.) dissolved in carbon disulphide (150 c.c.) with finely powdered aluminium chloride (10 g.) was cooled to 0°, and treated gradually (15 mins.) with a solution of acetyl chloride (7 g.) in carbon disulphide (10 g.). A smooth reaction took place, and the mixture was then kept for 2 hours at room temperature. After decomposition with cold dilute hydrochloric acid, the organic layer was separated, washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). After removal of the solvent, the greenish oily residue was submitted to vacuum-distillation. After some triphenylethylene (7 g.) had been recovered (mixed with traces of a green impurity), a fraction, b. p. 261—262°/10 mm., was collected; it solidified on standing, and was crystallised twice from alcohol–benzene, giving 1 : 1-*diphenyl*-2-p-*acetylphenylethylene* (8 g.) as fine, silky, colourless needles with a greenish shade, m. p. 125°, which dissolved in sulphuric acid with a yellow halochromic coloration (Found : C, 88·1; H, 6·2. $C_{22}H_{18}O$ requires C, 88·2; H, 6·0%). A solution of this ketone (2·2 g.) in alcohol (30 c.c.) was refluxed during 24 hours with hydroxylamine hydrochloride (1·6 g.) and sodium carbonate (1·1 g.) dissolved in water (5 c.c.). After cooling, the mixture was poured into an excess of water, and the solid precipitate collected, and twice recrystallised from alcohol; the *oxime* (2 g.) formed colourless prisms, m. p. 160° (Found : N, 4·6. $C_{22}H_{19}ON$ requires N, 4·4%), which dissolved in sulphuric acid with an intense yellow coloration.

1 : 1-*Diphenyl*-2-p-*acetamidophenylethylene.*—The foregoing oxime (0·3 g.) was dissolved in a mixture of glacial acetic acid (2 c.c.) and sulphuric acid (2 c.c.), and the solution heated al 95—100° until the yellow halochromic coloration disappeared (10 mins.). After cooling, the mixture was poured into ice-water; the flocculent precipitate obtained was collected, thoroughly washed with water, and recrystallised twice from alcohol, giving 1 : 1-*diphenyl*-2-p-*acetamidophenylethylene* (0·2 g.) in colourless prisms, m.p. 202—203° (decomp.) (Found : N, 4·2. $C_{22}H_{19}ON$ requires N, 4·4%). Alkaline saponification of this amide afforded 1-*p*-aminotriphenylethylene, which could not be obtained pure owing to its great solubility in alcohol and benzene.

Propionylation of Triphenylethylene.—The Friedel–Crafts reaction between triphenylethylene (12 g.), propionyl chloride (4·5 g.), and aluminium chloride (6 g.) was performed in carbon disulphide (120 c.c.) in the same manner as described above. 1 : 1-*Diphenyl*-2-p-*propionylphenylethylene* (6·5 g.) was obtained as a viscous, yellowish oil, b. p. 267—268°/10 mm., which slowly solidified on cooling, and formed fine, silky, colourless needles, m. p. 85°, from alcohol (Found : C, 88·7; H, 6·5. $C_{23}H_{20}O$ requires C, 88·4; H, 6·4%). The *oxime* (0·7 g.), obtained from the ketone (0·8 g.), hydroxylamine hydrochloride (0·55 g.), and sodium carbonate (0·3 g., dissolved in a few drops of water) in alcohol (25 c.c.), crystallised from alcohol in brilliant, colourless plates, m. p. 155° (Found : N, 4·6. $C_{23}H_{21}ON$ requires N, 4·3%). Beckmann's transformation, performed upon this oxime in the same way as for the lower homologue, yielded 1 : 1-*diphenyl*-2-p-*propionamidophenylethylene*, which formed minute colourless needles, m. p. 147° (sintering above 140°), from dilute aqueous alcohol (Found : N, 4·2. $C_{23}H_{21}ON$ requires N, 4·3%).

1 : 1-*Diphenyl*-2-p-n-*valerylphenylethylene.*—Triphenylethylene (12 g.), *n*-valeryl chloride (5·6 g.), and aluminium chloride (6·5 g.) were condensed in carbon disulphide (120 c.c.) as above, giving a liquid *ketone* which could not be induced to crystallise. After two redistillations in a vacuum, it formed a thick, yellowish oil (5 g.), b. p. 274—276°/10 mm., $n_D^{13°}$ 1·6570 (Found : C, 88·2; H, 7·2. $C_{25}H_{24}O$ requires C, 88·3; H, 7·0%), which did not solidify even after 6 months. The corresponding oxime also could only be obtained as an oil.

1 : 2-*Diphenyl*-1-p-*chlorophenylethylene.*—The crude crystalline carbinol obtained from benzylmagnesium chloride and *p*-chlorobenzophenone was dehydrated by dissolution in warm anhydrous formic acid. After dilution with water, the yellow oil obtained was extracted with benzene, the benzene layer washed with an aqueous solution of sodium carbonate, then with water, and dried (Na_2SO_4). After removal of the solvent and vacuum-distillation of the residue, a yellow oil, b. p. 231—232°/10 mm., was obtained, which slowly solidified into a crystalline cake; 1 : 2-*diphenyl*-1-p-*chlorophenylethylene* (yield 80%) formed long, silky, colourless needles, m. p. 89°, from acetic acid (Found : C, 82·4; H, 5·3. $C_{20}H_{15}Cl$ requires C, 82·6; H, 5·2%). Treatment of this compound (5 g.) dissolved in carbon disulphide (25 c.c.) with bromine (2·8 g., dissolved in 5 c.c. of carbon disulphide) in the cold yielded 1-*bromo*-1 : 2-*diphenyl*-2-p-*chlorophenylethylene* (5 g.), which crystallised from glacial acetic acid in long, colourless, glistening prisms, m. p. 157° (Found : C, 65·0; H, 4·0. $C_{20}H_{14}ClBr$ requires C, 64·9; H, 3·7%).

1-*Phenyl*-1-p-*chlorophenyl*-2-p-*acetylphenylethylene.*—A Friedel–Crafts reaction was performed with the foregoing chlorotriphenylethylene (15 g.), acetyl chloride (5·5 g.), and aluminium chloride (7 g.) in carbon disulphide (120 c.c.) as with triphenylethylene. The resulting *ketone* was purified by vacuum-distillation b. p. 282°/10 mm.); after two recrystallisations from acetic acid and then from alcohol–benzene, it formed long, colourless needles, m. p. 137° (Found : C, 79·1; H, 5·2. $C_{22}H_{17}OCl$ requires C, 79·4; H, 5·1%). The corresponding *oxime* crystallised from alcohol in fine, silky, colourless needles, m. p. 148° (Found : N, 4·2. $C_{22}H_{18}ONCl$ requires N, 4·0%).

Acetylation of αβ-Diethylstilbene.—Friedel–Crafts condensation of αβ-diethylstilbene (15 g.) in carbon disulphide (150 c.c.) with acetyl chloride (6·5 g.) in the presence of aluminium chloride (9 g.) afforded an orange-red mixture; this was decomposed by ice-cold dilute hydrochloric acid, and the organic layer worked up in the usual manner. After two redistillations in a vacuum, p-*acetyl*-αβ-*diethylstilbene* (2 g.) was obtained as a pale yellow, viscous oil, b. p. 205—210°/10 mm. (Found : C, 86·7; H, 8·2. $C_{20}H_{22}O$ requires C, 86·3; H, 7·9%). The diethylstilbene used was prepared according to Ramart-Lucas and Anagnostopoulos (*Compt. rend.*, 1928, **186**, 1626), and is therefore probably a mixture of stereoisomers.

Nitration of Triphenylethylene.—A suspension of triphenylethylene (10 g.) in cold glacial acetic acid (40 c.c.) was treated dropwise with concentrated nitric acid (*d* 1·52; 7 c.c.), and the mixture thus obtained

was heated at 80° on a water-bath for 2—3 mins. The thick, crystalline mass, which set rapidly on cooling, was filtered off and thoroughly washed with water. After recrystallisation from acetic acid, and then from alcohol–benzene, 1 : 1-*diphenyl*-2-p-*nitrophenylethylene* (6·5 g.) formed pale yellow, silky needles, m. p. 173° (Found : N, 4·8. $C_{20}H_{15}O_2N$ requires N, 4·6%).

Nitration of 1 : 2-*Diphenyl*-1-p-*chlorophenylethylene.*—A solution of this compound (5 g.) in glacial acetic acid (40 c.c.) was treated with concentrated nitric acid (*d* 1·52; 3·5 c.c.) in the same manner as above. The *mononitro*-compound (2 g.) thus obtained was recrystallised three times from acetic acid and formed brilliant yellow prisms, m. p. 166° (Found : N, 4·4. $C_{20}H_{14}O_2NCl$ requires N, 4·1%).

Nitration of 1-*Brominated Triphenylethylenes.*—(a) A suspension of 1-bromotriphenylethylene (Y.59) (5 g.) in a mixture of glacial acetic acid (25 g.) and nitric acid (*d* 1·52; 4 c.c.) was heated for ½ hour on a water-bath at *ca.* 80°, then cooled; the resulting yellow precipitate was collected, washed with water, and recrystallised first from acetic acid and then from alcohol. 1-*Bromo*-2 : 2-*diphenyl*-1-p-*nitrophenylethylene* (2 g.) was thus obtained as long, glistening, yellow needles, m. p. 180° (Found : N, 3·8. $C_{20}H_{14}O_2NBr$ requires N, 3·6%).

(b) 1-*Bromo*-2-*phenyl*-2-p-*chlorophenyl*-1-p-*nitrophenylethylene* (0·8 g.) was similarly obtained from 2 g. of the un-nitrated compound and concentrated nitric acid (2 c.c.); after crystallisation from glacial acetic acid, and then from alcohol, it formed fine, bright yellow, prismatic needles, m. p. 163° (Found : N, 3·5. $C_{20}H_{13}O_2NClBr$ requires N, 3·3%).

The reduction of those nitro-derivatives will be described later.

We wish to acknowledge our great indebtedness to Prof. Gley and the Roussel Laboratories in Paris for the biological assay of the above-mentioned compounds.

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213. *Amides. Part I. Preparation of Diacetimide.*

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The yield of diacetimide from acetamide and acetic anhydride is improved by dry hydrogen chloride, acetamide hydrochloride, or bisacetamide hydrochloride. Variation of the hydrogen chloride concentration between wide limits has little effect on the yield. The reaction between acetamide and acetic anhydride may proceed by two simultaneous mechanisms.

THIS investigation was undertaken as part of more extensive studies of the chemistry and biochemistry of amides. Previously described syntheses of diacetimide have the disadvantage of inconvenient operations and low yields. Diacetimide may be prepared by eliminating ammonia from two molecules of acetamide (Strecker, *Annalen*, 1857, **103**, 321; Rakshit, *J.*, 1913, **103**, 1557), by acetylating acetamide (Lindemann, *Sitz. Akad. Wiss. Wien*, Math.-natw. Kl., 1869, **60**, II. Abt., **53**; Franchimont, *Rec. Trav. chim.*, 1883, **2**, 344; Hentschel, *Ber.*, 1890, **23**, 2394; Titherley, *J.*, 1901, **79**, 391, 411; Dehn, *J. Amer. Chem. Soc.*, 1924, **34**, 1402), or by acetylating compounds related to acetamide such as acetonitrile (Gautier, *Compt. rend.*, 1868, **67**, 1256), *N*-acetyl-*N'*-methylurea (Hofmann, *Ber.*, 1881, **14**, 2731), and potassium cyanate or thiocyanate (Brunner, *Ber.*, 1914, **47**, 2671). Strecker, Lindemann, and Franchimont have reported very low yields in their syntheses. Hentschel investigated some of the causes of such low yields and devised a method which permits the preparation of diacetimide in useful quantities. The methods of Titherley, Rakshit, Brunner, and Dehn give comparable yields but at considerably higher cost. The authors have found that when Hentschel's method of reaction between acetamide and acetic anhydride is adopted and hydrogen chloride is used as a catalyst excellent yields of diacetimide are obtained. Hydrogen chloride may be introduced as dry gas or as one of the hydrochlorides of acetamide. A small amount of acetyl chloride has a similar effect but the yield is lower and the diacetimide is less pure than in the former cases. It is interesting to compare this modified Hentschel synthesis with the acetylation of hydrogen sulphide by acetic anhydride to thioacetic acid, which does not take place unless small quantities of hydrogen chloride or acetyl chloride are present (Clarke and Hartmann, *J. Amer. Chem. Soc.*, 1924, **46**, 1731).

Hentschel suggested that acetamide is acetylated by acetic anhydride. In the reaction catalysed by hydrogen chloride this is surely not the only process that takes place. Transient formation of ammonium chloride in early stages of the catalysed reaction is in better agreement with a mechanism in which ammonia is eliminated from two molecules of acetamide. Titherley (*loc. cit.*, p. 411) found that much bisacetamide hydrochloride is formed when acetamide is treated with acetyl chloride in boiling benzene solution and the yield of diacetimide is low. On completing Dehn's experiment of treating acetamide with acetyl chloride in cold ether, we found that the reaction proceeds almost quantitatively according to the equation $3NH_2Ac + AcCl = NHAc_2 + 2NH_2Ac,HCl$. When Titherley's experimental conditions were modified

by using boiling xylene instead of benzene, the yield of diacetimide increased and less acetamide was recovered in the form of bisacetamide hydrochloride. In other words, acetylation is favoured at low temperatures and condensation at higher temperatures. Further supports for the condensation theory and the comparative difficulty of acetylation are furnished by the observations that bisacetamide hydrochloride is not decomposed by refluxing with ethyl acetate but yields diacetimide when refluxed with amyl acetate, and that azeotropic acetylation of acetamide does not yield diacetimide. On the other hand, high yields of diacetamide obtained by the modified Hentschel process indicate that elimination of ammonia from 2 mols. of acetamide cannot be the only reaction and not less than one third of the available acetamide molecules must react by the acetylating process. Recent experiments on the synthesis of mixed diacylimides (to be published shortly) show that in some cases the principal process is acylation, and in others, elimination of ammonia from two amide molecules. The latter reaction may be initiated by the formation of oxonium compounds, which will be discussed more fully later.

Since a single mechanism is unlikely, it is best to state yields in terms of diacetimide obtained from 100 parts of acetamide. In the following table the column headed NH_2Ac shows the recovery of acetamide either in free form or as bisacetamide hydrochloride. Experiments marked *A* are original experiments; those marked with *B* refer to claims of previous authors. Previously described experiments which have been checked or repeated with only minor alterations are marked *C*.

No.	Reagents.	$NHAc_2$, as % of original	NH_2Ac, as % of original	Notes.
1 *B*	NH_2Ac–Ac_2O	50	—	$Ac_2O:NH_2Ac = 1·16:1$
2 *C*	do.	33	6	do.
3 *A*	$2HN_2Ac,HCl$–Ac_2O	90	2	$Ac_2O:NH_2Ac = 0·98:1$
4 *A*	do.	129	0	$Ac_2O:NH_2Ac = 1·29:1$
5 *A*	do.	95	10	HCl passed into Ac_2O
6 *A*	NH_2Ac,HCl–Ac_2O	124	3	$Ac_2O:NH_2Ac = 1·33:1$
7 *A*	NH_2Ac–$2NH_2Ac,HCl$–Ac_2O	120	0	$HCl:NH_2Ac = 1:12$
8 *A*	NH_2Ac–AcOH–BuOAc	0	45	Azeotropic distilln.
9 *A*	$2NH_2Ac,HCl$–EtOAc	0	100	—
10 *A*	$2NH_2Ac,HCl$–AmOAc	18	4	—
11 *B*	NHNaAc–AcCl	78	—	—
12 *B*	NH_2Ac–AcCl	17—21	—	In boiling benzene
13 *C*	do.	42	9	In boiling xylene
14 *C*	do.	34	80	In ether
15 *C*	do.	14	74	In benzene
16 *B*	NH_2Ac–Na–alc. HCl	[Overall yields not clearly stated]		
17 *B*	KOCN–Ac_2O	60—80	—	Yield as % of KOCN
18 *B*	KSCN–Ac_2O	32	—	Yield as % of KSCN

1, 2; Hentschel, *loc. cit.* 11; Titherley, *J.*, 1901, **79**, 391. 12, 13; *Idem*, *ibid.*, p. 411. 14, 15; Dehn, *loc. cit.* 16; Rakshit, *loc. cit.* 17, 18; Brunner, *loc. cit.*

The advantage of laboratory methods based on experiment 7 is obvious. Comparatively large quantities of diacetimide have been prepared by this method.

Experimental.

In order to save space no details are given for experiments checking previously published methods or for the purification of well-known reagents. Numbers preceding experiments refer to the table.

(3) Bisacetamide hydrochloride (Found: HCl, 23·24. Calc.: HCl, 23·62%), m. p. 128—135° (35 g.), was refluxed with freshly distilled acetic anhydride (45·4 g.) for 30 mins. Fractions boiling up to 125° were removed and the residue was distilled in a vacuum. The fraction of b. p. 104—106°/6 mm. was dissolved in 150 c.c. of ether. Dry hydrogen chloride precipitated some bisacetamide hydrochloride from this solution. The precipitate was filtered off, and the filtrate was freed from hydrogen chloride by treatment with barium carbonate (5 g.) and anhydrous potassium carbonate (5 g.) in succession. On removal of the ether, diacetimide (25 g.) was obtained; m. p. 78° (Found: N, 13·9. Calc.: N, 13·95%). Diacetimide (5 g.) was converted into sodium diacetimide by 30 mins.' refluxing with sodium (3 g.) in anhydrous ether (150 c.c.), 16 hours' standing, and another 30 mins.' refluxing. After filtration the ether was evaporated at 34°. No residue was obtained; hence the product was free from triacetamide.

(4) Bisacetamide hydrochloride (8·2 g.) and acetic anhydride (14·0 g.), treated as above, afforded 8·1 g. of diacetimide, m. p. 78°, free from triacetyl compound.

(5) Acetamide (30 g.) was suspended in acetic anhydride (64·5 g.). Dry hydrogen chloride was passed into the suspension until the weight increased by 9·3 g. The mixture was worked up as in the previous experiments, affording 28·5 g. of diacetimide, m. p. 78°, free from triacetyl compound.

(6) Acetamide (70 g.) was dissolved in about 350 c.c. of chloroform. The solution was treated with dry hydrogen chloride for 2½ hours. The precipitated crystals were filtered off and dried by suction; yield, 113 g. (Found: HCl, 34·9. Calc. for NH_2Ac,HCl: Cl, 38·2%). When a small sample (0·7 g.) was kept in 150 c.c. of chloroform for 3 hours, the HCl content was reduced to 33·0%. Freshly prepared

acetamide hydrochloride (10·0 g.) and acetic anhydide (14·0 g.) were treated as in previous experiments, yielding 8·1 g. of diacetimide, m. p. 78°, and 0·2 g. of bisacetamide hydrochloride.

(7) Acetamide (30·0 g.), bisacetamide hydrochloride (7·5 g.), and acetic anhydride (75·6 g.) were treated as in previous experiments, affording 42·8 g. of diacetimide; no bisacetamide hydrochloride was formed. Acetamide (200 g.), acetic anhydride (408 g.), and bisacetamide hydrochloride (20 g.) were worked up as in previous experiments but the crude product was collected at 105—112°/10 mm. Hardly any bisacetamide hydrochloride was formed. The residue from the ether was redistilled at 104—106°/7 mm., some material being discarded during the final distillation to safeguard purity (m. p. 79°; content of triacetyl component less than 0·005%). Crude yields varied between 240 and 280 g., and those of pure diacetimide between 200 and 240 g. When acetyl chloride (20 g.) was used instead of bisacetamide hydrochloride, 180 g. of diacetimide, m. p. 76—77°, were obtained. Much acetonitrile and high-boiling residue were formed.

(8) Acetic acid (204 g.) and *n*-butyl acetate (183 g.) were slowly distilled through a 4 ft. fractionating column. After 50 c.c. had been distilled off without evidence of water coming over, acetamide (100 g.) was added to the mixture and distillation was continued for six hours at a constant b. p. of 124°. The residue was worked up by the usual procedure. No diacetimide was obtained.

(9) Bisacetamide hydrochloride (30·0 g.) and ethyl acetate (62 c.c.) were refluxed for 20 hours. No change occurred.

(10) Bisacetamide hydrochloride (20·0 g.) and technical *iso*amyl acetate (b. p. 120—140°) (100 g.) were refluxed for 2 hours. Ammonium chloride (5·6 g.) was filtered off. The residue was worked up in the usual manner and yielded acetamide (0·5 g.), bisacetamide hydrochloride (0·3 g.), and diacetimide (2·8 g.).

(13) Acetamide (18 g.), acetyl chloride (26 g.), and xylene (100 c.c.) were heated under reflux for 60 mins. Fractionation yielded ammonium chloride (3·0 g.), bisacetamide hydrochloride (2·2 g.), and diacetimide (7·5 g.; m. p. 72—74°). 0·1 G. of an unidentified low-melting substance, not acetamide or diacetimide, was obtained from a fraction of b. p. 60—100°/8 mm.

(14, 15) Acetamide (18 g.) and acetyl chloride (8 g.) were mixed in ether (200 g.) or benzene (100 c.c.), kept for 2½ hours, heated for 10 mins. near the b. p. of the solvent, and then set aside for 3 days. Crystals of bisacetamide hydrochloride were obtained by filtering and washing with warm chloroform. The chloroform removed unreacted acetamide. More unreacted acetamide was precipitated by dry hydrogen chloride from the original solutions. Removal of the solvents gave diacetimide of poor quality, m. p. 40—50°. Total yields: bisacetamide hydrochloride, 15·3 g. from ether and 15·5 g. from benzene; unreacted and undissolved acetamide, 2·0 g. from ether, 1·4 g. from benzene; dissolved acetamide precipitated as bisacetamide hydrochloride, 0·5 g. from ether, 0·1 g. from benzene; impure diacetimide, 6·1 g. from ether, 2·5 g. from benzene. The reaction in benzene yielded acetonitrile, which was not isolated.

UNIVERSITY OF TASMANIA, HOBART. [*Received, July 7th*, 1947.]

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214. *The Adsorption of Water Vapour on Insulin and Plasma Albumin.*

By R. A. ROBINSON.

(1) By slight modifications of the isopiestic method of determining the vapour pressures of aqueous solutions, adsorption isotherms of water vapour on proteins can be determined in a short time.
(2) The adsorption of water vapour on insulin and on a plasma albumin has been measured.
(3) The Brunauer–Emmett–Teller adsorption equation can be used to express the results.
(4) The first, firmly bound, adsorbed layer corresponds to one molecule of water to each polar group in the protein molecule.

IN a recent paper Bull (*J. Amer. Chem. Soc.*, 1944, **66**, 1499) described the adsorption isotherms of water vapour on a number of proteins. Although his technique required twelve or more days for equilibrium to be reached between the vapour and the solid phase, the value of his results suggested that any method of accelerating the attainment of equilibrium would be of considerable help in expanding our knowledge in this field. Using two proteins, crystalline insulin and a crystalline bovine plasma albumin as adsorbents, it has now been found, by means of Robinson and Sinclair's isopiestic method (*ibid.*, 1934, **56**, 1830), that equilibrium could be reached in one or, at the most, two days.

EXPERIMENTAL.

Samples of the proteins, each about 1 g., were contained in flat-bottomed silver dishes along with another silver dish which contained a saturated salt solution to determine the humidity or water activity, a_w, and a platinum dish containing standardised sulphuric acid. From the gain or loss in weight of the acid the concentration at equilibrium could be calculated and hence the water activity from the tables of Shankman and Gordon (*ibid.*, 1939, **61**, 2370). The dishes rested on a thick copper block in a desiccator which could be evacuated and rocked in a thermostat. The heavy mass of metal served to smooth out small variations in the temperature of the thermostat and to facilitate the transfer of heat from one dish to another during the distillation. Except at the highest humidities, equilibrium was reached in 24

hours. From the change in weight of the protein sample its water content in equilibrium with sulphuric acid of known a_w could be calculated provided its original water content was known (see below). The insulin was obtained from the Fine Chemical Department of Messrs. Boots Pure Drug Co., Ltd.; it was listed as Batch Z11356, with a moisture content of 9·66% and ash 1·66%, identical with the specimen used by Chibnall, Rees, and Williams (*Biochem. J.*, 1943, **37**, 354). When received, however, its water content had risen to 10·85%. The bovine plasma albumin was a product of Armour and Co., Lot 46, with a moisture content of 4·23% and ash 0·15%; an analysis on a similar preparation is reported by Brand, Kassell, and Saidel (*J. Clin. Invest.*, 1944, **23**, 437). On receipt, however, its moisture content was 16·81%.

To determine the moisture content of the proteins they were rocked in the desiccator along with phosphoric oxide, the loss in weight being determined each day and the oxide renewed. This gave the moisture content on drying in a vacuum over phosphoric oxide at 25°. The following results were obtained:

Time (days)	1	2	3	4	5
Loss, %: insulin	10·24	10·46	10·55	10·82	10·85
,, albumin	14·35	14·67	16·44	16·81	16·81

The final weight was taken as the "dry weight" of the protein and all subsequent water contents will be expressed as g. of water per 100 g. of this dry protein.

To determine the time required to attain equilibrium, these dried samples of insulin and albumin were equilibrated with saturated calcium chloride ($a_w = 0·2963$), the approach to equilibrium being measured on successive days. The samples were then allowed to take up large quantities of water by distillation from a dish containing water, and then brought back to equilibrium with saturated calcium chloride solution. In this way the same point was approached by adsorption and desorption, with the results shown in Table I. This experiment shows that equilibrium is reached very rapidly by adsorption but slowly by desorption, and that hysteresis occurs.

TABLE I.

	G. of H_2O per 100 g. of protein.			
	Insulin.		Albumin.	
Time (days).	Adsorption.	Desorption.	Adsorption.	Desorption.
0	0	21·45	0	25·42
1	6·63	8·92	8·11	10·06
2	6·57	8·92	8·10	10·00
3	6·58	8·87	8·17	9·87
4	6·58	8·75	8·16	9·80

To obtain the adsorption isotherms, the samples were again dried over phosphoric oxide and allowed to adsorb water vapour in small increments. The results are given in Table II. After these measurements, the proteins were allowed to take up water vapour at $a_w = 1$ and this was then slowly

TABLE II.

Adsorption isotherms of insulin and albumin at 25°.

	Insulin. G. H_2O/100 g. protein:						Albumin. G. H_2O/100 g. protein:					
a_w.	Obs.	Calc.	a_w.	Obs.	Calc.		a_w.	Obs.	Calc.	a_w.	Obs.	Calc.
0·0310	1·88	1·38	0·3542	7·52	7·50		0·0310	2·15	1·85	0·3219	8·16	8·01
0·0960	3·31	3·20	0·4252	8·73	8·74		0·0590	2·89	2·94	0·3765	8·78	8·96
0·1115	3·65	3·53	0·4949	10·08	10·09		0·0705	3·42	3·30	0·4236	9·79	9·86
0·1695	4·47	4·59	0·5115	10·29	10·44		0·0946	4·04	3·95	0·4921	10·93	11·28
0·1766	4·70	4·71	0·6460	13·29	13·56		0·1147	4·45	4·41	0·5787	13·08	13·33
0·2213	5·38	5·42	0·6712	13·74	14·22		0·1695	5·36	5·48	0·6801	16·08	16·06
0·2263	5·53	5·50	0·7097	14·91	15·23		0·1766	5·47	5·60	0·7528	18·62	18·15
0·2595	6·07	6·01	0·7323	15·77	15·82		0·2627	7·05	7·03	0·8371	23·17	20·65
0·2627	6·05	6·06	0·8300	19·60	18·47		0·2963	7·67	7·59	0·8727	25·78	21·60
0·2963	6·58	6·58										

desorbed, with the results given in Table III. Hysteresis, as measured by the difference in the adsorption and the desorption curves, occurs at all water activities except the very lowest and, presumably, at $a_w = 1$. Over most of the a_w range it amounts to a difference of about 2·3 g. of water per 100 g. of either protein.

In addition, the author has determined a number of isotherms, starting, not with dried proteins, but with material dehydrated to different values of a_w. Such adsorption isotherms are always higher than those of the thoroughly dried material. As the proteins are prepared by partial dehydration, the isotherms naturally start at a point on the higher desorption isotherm and with increasing a_w tend towards the lower adsorption isotherm of the fully dried protein. This trend toward the lower curve is more marked, the lower the initial a_w. These isotherms would seem to have little significance; it is the adsorption isotherm of the properly dried protein which is important, and, perhaps, the desorption isotherm, although the latter must suffer from some inaccuracy because of the time required to attain equilibrium. Indeed, it is possible that no desorption process does correspond to true equilibrium.

TABLE III.

Desorption isotherms of insulin and albumin at 25°

Insulin. (G. of water per 100 g. of protein.)						Albumin. (G. of water per 100 g. of protein.)					
a_w.	Loss.	a_w.	Loss.	a_w.	Loss.	a_w.	Loss.	a_w.	Loss.	a_w.	Loss.
0·0265	2·35	0·1909	6·58	0·5020	12·37	0·0185	2·44	0·2132	7·75	0·5020	13·60
0·0300	2·50	0·2728	8·06	0·6851	16·23	0·0644	4·09	0·2728	9·15	0·6851	18·27
0·0470	3·21	0·2963	8·75	0·7402	17·95	0·0948	4·64	0·2963	9·80	0·7402	20·37
0·0947	4·48	0·3526	9·85	0·8417	21·40	0·1461	6·14	0·3526	10·80	0·8417	24·85

DISCUSSION.

According to the adsorption theory of Brunauer, Emmett, and Teller (*J. Amer. Chem. Soc.*, 1938, **60**, 309), if an infinite number of layers are available for filling as the water activity increases, the amount of water adsorbed (x) is related to the water activity (a_w) by

$$a_w/(1 - a_w)x = 1/X_mC + (C - 1)a_w/X_mC$$

where X_m is the number of g. of water (per 100 g. of protein) in the first unimolecular layer and $C \approx \exp.(E_1 - E_L)/RT$, $(E_1 - E_L)$ being the difference of the energy of adsorption in the first layer and the latent heat of evaporation. If, however, adsorption is limited to n layers the formula becomes

$$a_w/(1 - a_w)X = (1 - a_w + Ca_w - Ca_w^{n+1})/[1 - (n + 1)a_w^n + na_w^{n+1}]X_mC$$

which reduces to the simpler equation for small values of a_w.

A plot of $a_w/(1 - a_w)x$ against a_w for both proteins is linear up to $a_w = 0{\cdot}3$, so the constants X_m and C can be evaluated. By trial, a value of n is then found which fits the adsorption isotherm at higher values of a_w. By the method of least squares, the data for insulin gave $X_m = 5{\cdot}81$ g. of water per 100 g. of protein, $C = 9{\cdot}35$, and $(E_1 - E_L) = 1320$ cals./mol. For the albumin, $X_m = 6{\cdot}38$, $C = 12{\cdot}18$, $(E_1 - E_L) = 1480$. In each case $n = 7$, although a value of 6 would fit almost as well. The values of x calculated with the aid of these constants are given in Table II.

The desorption isotherms can be fitted to Brunauer, Emmett, and Teller's equation by the values $X_m = 6{\cdot}88$, $C = 16{\cdot}25$ for insulin, and $X_m = 7{\cdot}75$, $C = 14{\cdot}67$ for the albumin.

The constants for the adsorption isotherm may now be compared with the number of polar side-chain groups along the lines suggested by Pauling (*ibid.*, 1945, **67**, 555). If we assume from Chibnall's data (*J. Intern. Soc. Leather Trades Chem.*, 1946, **30**, 1) that a submolecular unit of insulin of weight 12,000 contains the following polar constituents: arginine, 2; histidine, 4; lysine, 2; glutamic acid, 15; aspartic acid, 5; tyrosine, 9; serine, 6; threonine, 2; proline, 3, and that the twelve amide nitrogen atoms are attached to the carboxyls of glutamic and aspartic acid, we are left with 36 polar groups. If each of these can take up one water molecule, then the amount of water in the unimolecular layer should be 5·4 g. per 100 g. of protein (obs. 5·8). For the bovine albumin Branch, Kassell, and Saidel's analysis (*loc. cit.*) corresponds to 6·6 g. per 100 g. of protein (obs. 6·4).

I wish to express my thanks to Dr. J. A. V. Butler for much valuable advice as well as the gift of the plasma albumin, to Messrs. Boots Pure Drug Co., Ltd., for the insulin specimen, and to the Chemical Society for a grant from their Research Fund.

UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, August 11th*, 1947.]

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215. *The Problem of Molecular Asymmetry based on Isotopic Differentiation of Hydrogen. An Attempted Asymmetric Synthesis by the Marckwald Method.*

By D. J. G. IVES and (Miss) M. R. NETTLETON.

The Marckwald method has been applied to attempt the asymmetric synthesis of R·CHD·CO_2H, where R = benzyl, ethyl, or *n*-butyl, by the decarboxylation under mild conditions of brucine, nicotine, and bornyldimethylamine acid salts of the correspondingly substituted malonic dideuteracids, but no significant optical activity has been found in the products.

ATTEMPTS to obtain optically active compounds of the type $CHDR_1R_2$ or $CR_1R_2R_HR_D$, where R_D differs from R_H only by the substitution of deuterium for hydrogen, have not hitherto been successful, and the question of whether molecular asymmetry of this kind, due solely to isotopic differentiation of hydrogen, can give rise to observable optical activity still remains open. The lack of optical equivalence of the isotopes, shown particularly by significant differences of rotatory power between pairs of active compounds $CR_1R_2R_3R_H$ and $CR_1R_2R_3R_D$ (cf., *inter alia*, Erlenmeyer and Schenkel, *Helv. Chim. Acta*, 1936, **19**, 1199; Young and Porter, *J. Amer. Chem. Soc.*, 1937, **59**, 328, 1437), suggests that the reasons for failure to reach a decision on this problem may be experimental rather than fundamental. Such reasons might be inadequate differences in solubility of diastereoisomerides identical except in isotopic configuration, racemisation caused by too drastic conditions of chemical reaction, and, very generally, insensitivity of tests for activity because of very small yields of products which, at best, are likely to show only a minute rotation. The Marckwald asymmetric synthesis appeared likely to avoid these difficulties, since, by its use, substituted deuteroacetic acids may be generated under asymmetric, chemically mild conditions in amounts sufficiently large to allow very careful purification and high sensitivity of tests for optical activity. Accordingly, the method was applied by decarboxylating at the lowest possible temperatures the acid salts of benzyl-, ethyl- and *n*-butyl-malonic dideuteracids with suitable optically active tertiary bases (brucine, nicotine, bornyldimethylamine), but no significant optical activity was detected in the products. The work is now briefly recorded because it embodied a new method of attack which was reasonably expected to have advantages over those previously used.

The work dealt mainly with β-phenyl-α-deuteropropionic acid, prepared by various modifications of the following scheme. Benzylmalonic ester was carefully fractionated and examined polarimetrically to ensure freedom from any fortuitous trace of optically active impurity, a precaution which was applied whenever possible to all materials and solvents used. The acid obtained by hydrolysing the ester was converted into its silver salt, which was suspended in dry ether and treated with the calculated volume of a standard solution of deuterium chloride in dry ether. Filtration in a closed apparatus and removal of solvent gave an 80—90% yield of the dideuteracid, of which the acid salt with the tertiary base was prepared under anhydrous conditions. According to Eisenlohr and Moiser (*Ber.*, 1938, **71**, 998), the production of a well-defined crystalline salt is essential for successful asymmetric synthesis, and efforts were therefore made to achieve decarboxylation without melting. For example, the acid bornyldimethylamine salt was largely decarboxylated in the course of 70 hours at a temperature below 70°. In another experiment, the base was continuously removed in vacuum during decarboxylation which occupied 13 days at a maximum temperature of 66°. It was observed that the bornyldimethylamine salt, when formed, appeared partly as a crystalline solid and partly as an oil: these two fractions were rapidly separated and independently decarboxylated. The substituted propionic acid was isolated by the usual means and purified from residual traces of active base by extraction in alkaline solution with ether or chloroform and distillation in a high vacuum. Polarimetric readings were usually taken with a 60—70% solution in benzene in a 4-dm. tube of 8 c.c. capacity, and random variation was minimised as far as possible by averaging large numbers of individual observations. The pure, fused acid and solutions of the acid in pyridine, ethanol, and dioxan were also examined. In all cases, experiments were duplicated throughout by an exactly similar sequence of operations with the hydrogen compounds, in order to provide a rigid control to check any small activity that might be observed. Various experimental modifications were tried, including the preparation of malonic deuteracids by the action of water on the malonyl chlorides; this was found to be unsatisfactory.

The results are summarised in the following table, which includes only those experiments considered to be most satisfactory and sensitive as tests for activity in the products.

Acid.	Base.*	$[\alpha]_D$.	$[\alpha]_{5461}$.	Conditions.
$CH_2Ph{\cdot}CHD{\cdot}CO_2H$	Brucine	0·006°	0·007°	67·3% in C_6H_6, $l = 4$
,, ...	Nicotine	0·006	—	72·0% in C_6H_6, $l = 4$
,, ...	B.D.M.A.	0·006	−0·005	60·3% in C_6H_6, $l = 4$
,, ...	,,	0·030	−0·046	Fused, 48·5°, $l = 2$
$CH_2Ph{\cdot}CH_2{\cdot}CO_2H$	,,	−0·004	—	66·1% in C_6H_6, $l = 4$
,, ...	,,	0·025	0·029	Fused, 48·5°, $l = 2$
$CHDEt{\cdot}CO_2H$	Brucine	−0·016	−0·018	Pure, $l = 2$
$CH_2Et{\cdot}CO_2H$	,,	−0·031	−0·032	,, ,,
$CH_2Et{\cdot}CHD{\cdot}CO_2H$	B.D.M.A.	0·020	—	,, $l = 1$
$CH_2Et{\cdot}CH_2{\cdot}CO_2H$	,,	−0·015	—	,, ,,

* B.D.M.A. = bornyldimethylamine.

Unless otherwise stated, all rotations were observed at room temperature. It will be noted that in all those cases where the specific rotation exceeds 0·01°, the corresponding control shows an equal or greater activity, which must be attributed solely to special difficulty in purification or rotation.

Experimental.

(+)-*Bornylamine Hydrochloride.*—Camphoroxime was reduced by sodium in amyl alcohol (Forster, *J.*, 1898, **73**, 390), and the product separated from the accompanying *neo*bornylamine by repeated crystallisation of the hydrochloride from dilute hydrochloric acid; $[\alpha]_D^{18}$ 22·96° (c = 3·895 in ethanol).

(+)-*Bornyldimethylamine.*—(+)-Bornylamine hydrochloride (60 g.) was reductively condensed with formaldehyde (100 c.c. of 40%) by shaking the aqueous solution (500 c.c.) containing sodium acetate (3 g.) and palladised charcoal in an atmosphere of hydrogen. After removal of the catalyst and excess of formaldehyde the base was liberated and obtained as a water-white liquid by distillation under reduced pressure; b. p. 104°/8 mm.; $d_4^{22°}$ 0·8976; $[\alpha]_D^{22°}$ 34·86°, $[\alpha]_{5461}^{22°}$ 42·18°). (Forster, *J.*, 1898, **73**, 944, gives $[\alpha]_D^{16°}$ 62·5°, but his product undoubtedly contained the monomethylamine as impurity.)

Brucine.—Commercial brucine was treated in hydrochloric acid solution with activated charcoal, and the acid solution extracted repeatedly with ether. The liberated base was recrystallised five times from 25% aqueous ethanol and dried in a vacuum; m. p. 178—179°; $[\alpha]_D^{17·5°}$ − 122° (c = 1·893 in chloroform).

Nicotine.—The commercial product was purified by recrystallisation of the double salt with zinc chloride from ethanol (Lowry and Lloyd, *J.*, 1929, 1381). The liberated base was dried over potassium hydroxide and distilled under reduced pressure of hydrogen; b. p. 83°/1·7 mm.; α_D − 83·6° (l = 0·5).

Diethyl Benzylmalonate.—This ester was prepared by the usual methods, carefully fractionated (b. p. 117°/0·8—0·9 mm.), and examined for optical activity; α_D 0·00°; α_{5461} 0·00° (l = 4).

Benzylmalonic Acid.—The acid obtained by hydrolysis of the above ester was recrystallised from "AnalaR" benzene; m. p. 120° (Found: equiv. by titration, 97·1. Calc. for $C_{10}H_{10}O_4$: equiv., 97·09); α_D 0·00°, α_{5461} 0·00° (l = 4, c = 33·2% in ethanol).

Silver Benzylmalonate.—Benzylmalonic acid was treated with 1 equiv. of sodium hydroxide solution, and the sodium salt precipitated and washed with alcohol and dried in vacuum (Found: Na, 19·32. Calc. for $C_{10}H_8O_4Na_2$: Na, 19·33%); α_D 0·00°, α_{5461} 0·00° (l = 4, c = 28·3 in water). An attempt to prepare benzylmalonic dideuteracid directly from the sodium salt by the action of DCl in dry ether failed, owing to the formation of a stable gel of sodium chloride. The silver salt was prepared by treating the sodium salt in aqueous solution with 1 equiv. of silver nitrate. The precipitated salt was thoroughly washed with water and acetone and dried in a vacuum, with protection from the action of light (Found: Ag, 52·71. Calc. for $C_{10}H_8O_4Ag_2$: 52·89%).

Benzylmalonic Dideuteracid.—The above silver salt was suspended in ether (dried over sodium, phosphoric oxide, and redistilled) with vigorous mechanical stirring, and a solution of deuterium chloride (1 equiv.) slowly added. The reagent was prepared by dropping deuterium oxide slowly on an excess of phosphorus pentachloride in a small water-cooled vessel and leading the issuing gas successively through a tube packed with phosphorus pentachloride, two traps cooled to − 60°, and a large spiral condenser at − 60° into an absorption vessel consisting of a large bulb, leading by means of a ground-in delivery tube to a calibrated tap-funnel containing dry ether. After generation and absorption of a slight excess of DCl, a portion of the ethereal solution was titrated with standard alkali. The required volume of solution was then used in the silver salt decomposition, which was complete in about an hour. The resulting ethereal solution of the deuteracid was removed by suction through a coarse filter stick into a large sintered-glass filter, the whole apparatus being enclosed and protected from ingress of moisture. The filtrate was evaporated under reduced pressure, and the *deuteracid* obtained in 85—90% yield as a snow-white crystalline residue which was dried in a vacuum; m. p. 119—122° (Found: $D_2O + H_2O$, by combustion, 46·0, 46·9; D, 1·89, 1·95; equiv., by titration, 97·9, 98·1, 98·2. $C_{10}H_8D_2O_4$ requires $D_2O + H_2O$, 46·9; D, 2·05%; equiv., 98·1). Deuterium estimations were carried out by density determinations on the combustion waters, as described by Ives (*J.*, 1938, 81).

β-Phenyl-α-deuteropropionic Acid.—(1) *Prepared by decarboxylation of the bornyldimethylamine acid salt of benzylmalonic dideuteracid.* (A) An ethereal solution of the base, in slight deficiency of ½ equiv., was added slowly to the acid dissolved in ether, with mechanical stirring. Ether was removed from the precipitated salt at room temperature, and the salt decarboxylated by heating under reduced pressure up to a maximum temperature of 110° in the course of 2½ hours. The residue was treated with alkali and repeatedly extracted with ether. The acid was liberated, extracted with ether, and recovered from the ethereal solution in 79% yield; m. p. 48—49° (Found: $D_2O + H_2O$, by combustion, 60·9; D, 1·59; equiv., by titration, 151·1. $C_9H_9DO_2$ requires $D_2O + H_2O$, 60·25; D, 1·33%; equiv., 151·1). Slight optical activity was found in this product, examined in the fused state and in various solvents. A similar activity, however, was found in a control sample of β-phenylpropionic acid prepared in an exactly similar way from the same batch of silver benzylmalonate, and neither activity survived distillation of the acids in a high vacuum.

(B) The bornyldimethylamine salt, prepared as above, was allowed to stand in ether overnight in order to become fully crystalline; it was decarboxylated in 8½ hours at a maximum temperature of 80°, purified as above and distilled at 115—120°/0·1—0·2 mm.; α_D 0·03° (l = 4, c = 70·1% in benzene); m. p. 48—49° (Found: $D_2O + H_2O$, by combustion, 60·3; D, 1·39%; equiv., by titration, 151·1).

(C) The benzylmalonic dideuteracid was not isolated; the base in ethereal solution was added rapidly to the filtrate from the decomposition of the silver salt. The resulting salt was separated into two fractions, one oily and the other crystalline. Both these were decarboxylated rapidly at 110° and yielded inactive products.

(D) The bornyldimethylamine acid salt was prepared by use of exactly ½ equiv. of base and was decarboxylated in the course of 13 days at a maximum temperature of 66°. The vacuum in the apparatus was maintained, and the base, liberated during decarboxylation, was continuously removed and collected in a trap cooled at − 80°; 95% of the base was thus recovered. The acid was purified as

usual, and finally by distillation in high vacuum at 60°; m. p. 48—49°; α_D 0·00°, α_{5461} 0·00°, α_{4358} 0·01° ($l = 4$, $c = 60·3\%$ in benzene) (Found: equiv., by titration, 151·1).

(2) *Prepared by decarboxylation of the brucine acid salt of benzylmalonic dideuteracid.* ½ Equiv. of brucine in chloroform solution was added slowly to the acid, dissolved in ether, with mechanical stirring. The salt was left overnight to become fully crystalline, and the solvent removed at room temperature. Decarboxylation was carried out in a vacuum at a maximum temperature of 120° in the course of 20 hours. The resulting acid was purified by constant chloroform extraction in alkaline solution and by distillation in a high vacuum; m. p. 49—50°; α_D 0·00°, α_{5461} 0·00°, α_{4358} 0·01° ($l = 4$, $c = 67·3\%$ in benzene) (Found: equiv., by titration, 150·9).

(3) *Prepared by decarboxylation of the nicotine acid salt of benzylmalonic dideuteracid.* The salt, prepared in ethereal solution, separated as a viscid gum which could not be crystallised. The solvent was removed, and the vitreous residue decarboxylated in vacuum at 110° in the course of 18 hours. The product was purified by constant ether extraction in alkaline solution and by distillation in high vacuum; m. p. 48·5—49°; α_D 0·00° ($l = 4$, $c = 72·0\%$ in benzene) (Found: equiv., by titration, 151·5).

Ethylmalonic Dideuteracid.—This *acid* was prepared by the action of DCl on silver ethylmalonate (Found: Ag, 62·37. Calc. for $C_5H_6O_4Ag_2$: Ag, 62·39%) in the way already described; m. p. 107—109° (Found: equiv., by titration, 67·3. $C_5H_6O_4D_2$ requires equiv., 67·06).

α-Deuterobutyric Acid.—The acid brucine salt of ethylmalonic dideuteracid was prepared by adding ½ equiv. of brucine, in ethylene dichloride solution, to the acid dissolved in ether, with mechanical stirring. After one hour, the solvent was removed from the crystalline salt at room temperature. Decarboxylation was effected below the m. p. of the salt and occupied 20 hours at a maximum temperature of 150°. The vacuum was maintained during this process, and the α-deuterobutyric acid distilling was collected in a trap cooled to − 80°. The residue was treated separately and provided a much smaller portion of acid. The distilled sample was purified by constant extraction in alkaline solution with ethylene dichloride for 12 hours and vacuum distillation; b. p. 85·5°/40 mm. (Found: equiv., by titration, 89·85. $C_4H_7DO_2$ requires equiv., 89·12). A small activity was found in this sample (α_D − 0·02°, α_{5461} − 0·02°; $l = 2$), but a still greater rotation was given by the corresponding control, undeuterated acid. Both activities were reduced by distillation at 0° in a high vacuum, and were therefore clearly due to some acidic impurity derived from the brucine.

α-Deuterohexoic Acid.—Butylmalonic dideuteracid was prepared by the action of deuterium oxide on butylmalonyl chloride in ethereal solution. The acid bornyldimethylamine salt, obtained as a crystalline solid by the method already described, was decarboxylated in a vacuum at a maximum temperature of 125°. The α-deuterohexoic acid formed (b. p. 98°/9 mm.) was inactive. The butylmalonyl chloride required in this experiment was prepared by adding successive small amounts of butylmalonic acid to an excess of phosphorus pentachloride, with constant shaking. The mixture, which soon liquefied, was kept at room temperature for two days and then gently heated. The temperature was first raised to 60° during one week and finally to 100° for one hour. Repeated fractionation (some decomposition at first) afforded the acid chloride as a colourless liquid in 40% yield; b. p. 74—78°/4 mm. (Found: Cl, 36·0. Calc. for $C_7H_{10}O_3Cl_2$: Cl, 36·0%). Benzylmalonyl chloride was prepared in 75% yield as a yellow oil, b. p. 135—136°/7 mm. (Found: Cl, 31·0. Calc. for $C_{10}H_8O_3Cl_2$: Cl, 30·7%), by a similar method, which was found to be the only workable procedure; others appeared to lead to tarry products or mixtures of acid chloride with anhydride.

The authors record their warm thanks to Dr. F. Barrow, at whose suggestion this work was undertaken, for his constant interest and help.

BIRKBECK COLLEGE, E.C. 4. [*Received, August 11th*, 1947.]

NOTE.

2-*Methoxy*mesobenzanthrone.

By FAWZY GHALI BADDAR.

THE synthesis of 2-methoxy*meso*benzanthrone (the important intermediate for Caledon Jade Green) is covered by several patents, but no practical details are given. The author now reports favourable conditions for its preparation. 3-Amino*meso*benzanthrone (cf. Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 285) was acetylated with acetic anhydride to 3-acetamido*meso*benzanthrone which, on nitration with fuming nitric acid in acetic acid solution, gave 2-nitro-3-acetamido*meso*benzanthrone (I), and this was hydrolysed with alcoholic sulphuric acid to the amine (II). This gave on diazotisation with sodium nitrite and sulphuric acid a diazo-oxide, which on being refluxed with alcohol and aluminium powder, was reduced to 2-hydroxy*meso*benzanthrone (III) (cf. I. G. Farbenind. A.-G., D.R.-P. 436,525; *Centr.*, 1927, **98**, *I*, 182). The phenol (III) was then methylated to 2-methoxy*meso*benzanthrone (IV), which gave on fusion with potassium hydroxide, the green dye, Caledon Jade Green.

Experimental.—3-*Acetamido*mesobenzanthrone. 3-Amino*meso*benzanthrone was acetylated by either of two procedures: (i) The finely powdered base (7 g.) was thoroughly mixed with acetic anhydride (20 c.c.) and heated on the water-bath for 15 minutes; the acetyl derivative was precipitated with ether and crystallised from glacial acetic acid in brown-violet needles, m. p. 279—280°. (ii) The crude base (24 g.) was dissolved in boiling glacial acetic acid (700 c.c.), and the filtered solution treated with acetic anhydride (70 c.c.) and heated on the water-bath for one hour; on cooling, the acetyl derivative crystallised in brown-violet needles, m. p. 279—280° (Found: C, 78·9; H, 4·6; N, 5·0. Calc. for $C_{19}H_{13}O_3N$: C, 79·4; H, 4·6; N, 4·9%); yield, 95%. I.G. Farbenind. A.-G., (*loc. cit.*) and Farbwerke vorm. Meister Lucius and Brüning (E.P. 224,522; *Centr.*, 1926, **97**, I, 1717) give m. p.s 225° and 255° respectively.

2-*Nitro*-3-*acetamido*mesobenzanthrone (I). The solution of 3-acetamido*meso*benzanthrone (20 g.) in hot glacial acetic acid (1200 c.c.) was heated on the water-bath with stirring. A solution of fuming nitric acid (12 c.c.; *d* 1·486) in glacial acetic acid (80 c.c.) was quickly added, and the stirring continued for 15 minutes. The precipitated nitro-derivative was filtered off while hot, and washed with hot acetic acid. On crystallisation from nitrobenzene, 2-nitro-3-acetamido*meso*benzanthrone was obtained in yellow needles, m. p. above 318° (Found: C, 68·4; H, 3·7; N, 8·7. Calc. for $C_{19}H_{12}O_4N_2$: C, 68·7; H, 3·6; N, 8·4%); yield, 18·5 g. I. G. Farbenind. A.-G. (*loc. cit.*) give m. p. 306°.

2-*Nitro*-3-*amino*mesobenzanthrone. The acetyl derivative (5 g.) was dissolved in concentrated sulphuric acid (50 c.c.), and ethyl alcohol (250 c.c.) slowly added. The mixture was refluxed for 3—4 hours, and the product precipitated with water and filtered off. On crystallisation from nitrobenzene, 2-nitro-3-amino*meso*benzanthrone was obtained in orange-red crystals, m. p. 316—317°, depressed to 190—200° on admixture with (I) (Found: C, 70·3; H, 3·5; N, 9·4. Calc. for $C_{17}H_{10}O_3N_2$: C, 70·3; H, 3·5; N, 9·7%); yield nearly quantitative.

2-*Hydroxy*mesobenzanthrone (III). 2-Nitro-3-amino*meso*benzanthrone (3 g.) was dissolved in concentrated sulphuric acid (60 c.c.) and cooled in a freezing mixture. The solution was thoroughly stirred, and finely powdered sodium nitrite (1·2 g.) was added portionwise during one hour. During that time crushed ice (100 g.) was slowly added, so that the temperature was not allowed to rise above 20°, and the stirring was continued for a further hour. The product was then precipitated with a further amount of ice (100 g.), allowed to stand overnight, and the precipitated diazo-oxide was filtered off and dried (yield, 2·3 g.). Its alcoholic solution gave a blue coloration when mixed with resorcinol and treated with a drop of dilute sodium hydroxide solution.

The powdered diazo-oxide (2·3 g.) was suspended in alcohol (100 c.c.) and refluxed with aluminium-bronze for 9 hours (until it ceased to give a blue coloration with resorcinol). The alcohol was evaporated, and the residue extracted with boiling sodium hydroxide solution and filtered. The filtrate (charcoal) on acidification precipitated 2-hydroxy*meso*benzanthrone (yield, 1·1 g.) (cf. Farbwerke vorm. Meister Lucius and Brüning, F.P. 588,035; *Centr.*, 1926, **97**, I, 1051).

2-*Methoxy*mesobenzanthrone. The phenol (III) was dissolved in sodium hydroxide solution, warmed, and treated with methyl sulphate. The precipitated methoxy-compound crystallised from ethyl alcohol in brownish-yellow crystals, m. p. 174—174·5° (Found: C, 82·6; H, 4·7; OMe, 10·9. Calc. for $C_{18}H_{12}O_2$: C, 83·1; H, 4·7; OMe, 11·9%).—Fouad I University, Cairo, Egypt. [*Received, August 18th*, 1947.]

OBITUARY NOTICE.

FRANK CLIFFORD WHITMORE.

1887—1947.

FRANK CLIFFORD WHITMORE died suddenly at his home in State College on June 24th, 1947. He was research professor of organic chemistry and dean of the School of Chemistry and Physics at the Pennsylvania State College. He was an outstanding and versatile leader, an inspiring administrator and teacher, a tireless and skilful scientist, and a kind and helpful adviser. In addition to publishing more than 200 scientific and technical papers he was the author of two books : " Organic Compounds of Mercury " (1921) and " Organic Chemistry " (1937).

Whitmore was an authority on many phases of organic chemistry. His more recent work was in aliphatic and hydrocarbon chemistry and in molecular rearrangements. His electronic conception of intramolecular rearrangements and related reactions is now generally accepted; his ideas not only explain, as part of an orderly scheme, the hundreds of apparently random rearrangements which occur during the simplest replacement reactions, but they also predict the products which form as a result of a seemingly complicated series of organic reactions.

Fellow scientists honoured Whitmore in many ways. In 1938 he was awarded the William H. Nichols Medal for outstanding chemical work. The American Chemical Society elected him its president in 1938. The highest chemical honour in the nation, the Willard Gibbs Medal, was awarded him in 1945. In 1946 he was elected to the National Academy of Sciences. Four colleges honoured him with Doctor of Science degrees : Franklin and Marshall (1937), University of Delaware (1937), Allegheny (1938), and the Philadelphia College of Osteopathy (1943). He did both his undergraduate and graduate work at Harvard University, receiving his Ph.D. degree in 1914.

Whitmore was an inspiring and thorough teacher. He maintained rigid scholastic standards while holding the respect and goodwill of his students, and was always sympathetic toward the student who was making a real effort to learn. He was an excellent teacher of inorganic chemistry and showed great interest in inorganic work. Before coming to Penn State in 1929 he taught at Williams, Rice Institute, and the University of Minnesota, and he was chairman of the chemistry department at Northwestern University. At Penn State he taught freshmen, seniors, and graduate students, and conducted many seminars. He gave numerous talks to local sections and national meetings of the American Chemical Society, and did valuable work on the Society's unemployment, professional, and economic status committees. Between 1936 and 1940 he was an associate editor of the *Journal of the American Chemical Society*. For many years he was on the editorial board of *Organic Syntheses*, and was editor-in-chief of Volume VII (1927) and Volume XII (1932). He was an associate editor of " Science of Petroleum," and author of an article on molecular rearrangements for the 1946 " Encyclopaedia Britannica."

Whitmore was one of Penn State's great Deans. Despite greatly increased instructional and administrative duties during his deanship, he never lost any of his zest for life, for research, and for helping people. Under his administration the work in chemistry was accredited by the American Chemical Society, and that in chemical engineering by the American Institute of Chemical Engineers. He followed closely the progress in college of returning war veterans, and devoted a great deal of time to their scholastic programmes.

During the First World War, Whitmore worked at Rice Institute on poison gases and mercury compounds. During the Second World War he organized and supervised a group of 35 full-time instructors for the Army Specialized Training and Navy V-12 programmes of his School. The entire extensive research facilities of his School were made available to the armed forces. His own war-time research related to aviation fuels, special lubricants, super-explosives, antimalarials, synthetic rubber, penicillin, silicones, and camouflages. In all, he supervised in his School more than 30 war-time research projects and a staff of about 150 full-time workers. In addition, he served as consultant to many industrial groups and federal agencies, including the War Production Board, War Manpower Commission, National Defense Research Committee, Office of Production Research and Development, and Office of the Quartermaster General. Outstanding was the timely and vigorous, if unofficial, support that he gave wholeheartedly to those who tried to keep the Selective Service System really selective by putting chemists, physicists, and chemical engineers where they could do the most good in winning the war. He had strong convictions as to the need for training these scientists and retaining them in war-production and research work. This involved attending many meetings, writing many letters,

and filing many forms. In all, he personally wrote or filed more than 7,000 letters and forms which were sent to draft boards, government officials, and others interested in and responsible for the operation of the Selective Service System. This prodigious effort, more than any other factor, contributed to his untimely death.

Whitmore had long been interested in petroleum. Before coming to Penn State he had studied the sulphur compounds in petroleum, and his work in aliphatic chemistry was applied in many ways to new petroleum products or refining methods. While at Penn State he and his colleagues synthesised approximately 300 different hydrocarbons: these pure materials were invaluable as reference standards in many entirely new petroleum developments. He was director of the work being done at Penn State for American Petroleum Institute Research Projects 42, 43B, and 46 which were concerned respectively with high-molecular-weight hydrocarbons, the origin of petroleum, and hydrocarbons for spectrometer calibrations. His work on the rearrangement of organic compounds was very important in the manufacture of special high octane super-fuels for military aircraft. From 1929 he and his colleagues in the Petroleum Refining Laboratory had been carrying out a comprehensive research and development programme, as a result of which more is now known about the composition of Pennsylvania petroleum than any other crude oil in the world. He was active in helping the Pennsylvania petroleum industry to obtain methods for characterising and identifying Pennsylvania lubricants in order to protect the public from unfair trade practices, and was a vigorous proponent of the application of scientific and technical developments to the efficient utilisation of Pennsylvania petroleum. He guided the Schools' research and development work towards the modernisation of the state's oil industry, the adaptation of new processes to the refining of Pennsylvania petroleum, and the use of chemicals and additives for improving the quality of the products.

Apart from the fraternity organisations, a number of learned and professional societies honoured Dean Whitmore. The American Association for the Advancement of Science elected him vice-president in 1932. He was a member of the American Institute of Chemical Engineers, the Chemical Society of London, Deutsche Chemische Gesellshaft, American Academy of Arts and Sciences, the American Institute, the National Institute of Social Sciences, the Franklin Institute, the Cosmos Club of Washington, D.C., and the Chemists Clubs of New York and Chicago. He was elected president of the Pennsylvania Chemical Society in 1940, and in 1928 was appointed a director of the Institute of Chemistry.

His spontaneity, enthusiasm, sense of humour, and boundless energy made him the best of companions. He was always cheerful, inspiring, and even-tempered. His friends will always remember him for his unfailing interest in and continual devotion to their welfare.

Whitmore was born in North Attleboro, Mass., on October 1st, 1887. He was the son of Frank Hale and Lena Avilla Thomas Whitmore. In 1914, he married Marion Gertrude Mason of Cambridge, Mass., who survives with four children.

M. R. Fenske.

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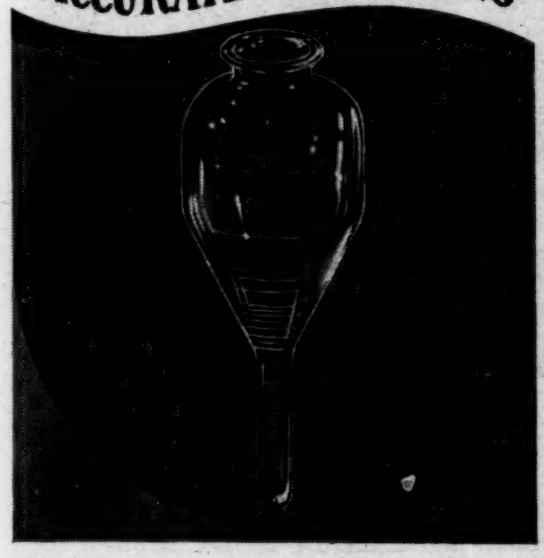

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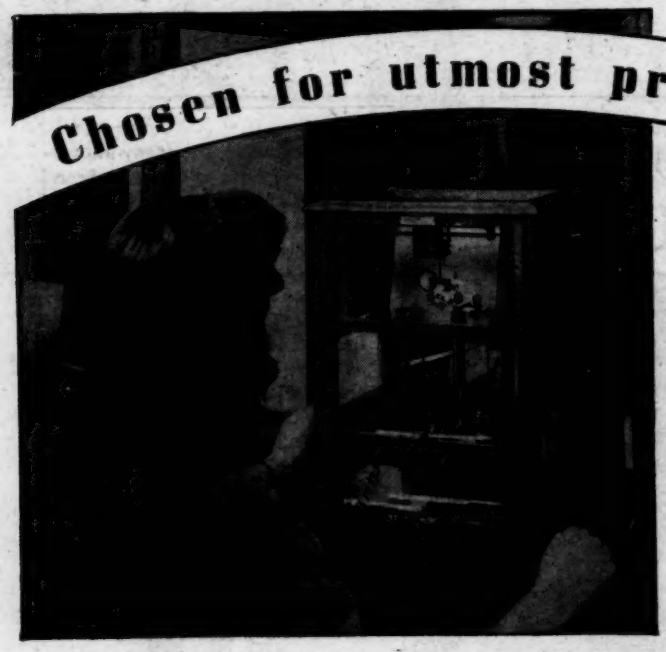

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